Placental Pathology

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Value of Placental Examination

- Etiology of intrauterine or perinatal death
- Etiology of preterm delivery
- Etiology of anomaly
- Etiology of neurologic impairment
- Alter management of future pregnancies
- Pathophysiology of maternal or neonatal disorders

Value of Placental Examination

- Immediately useful to neonatologists caring for sick infant
- Useful to pediatricians and parents later in infancy or childhood
- Reports usually go to obstetrician not pediatrician

1997 CAP Practice Guideline

All placentas be examined in delivery room

- Cord length, number of vessels, dimension, weight, integrity of maternal surface and membranes

Triaged for complete exam if they meet certain maternal, fetal or placental criteria

- Obstetric history, gestational age, mode of delivery, birth weight, sex, Apgar scores, maternal and fetal complications in pregnancy, labor and delivery, indications for exam

How well are CAP guidelines followed?

Spencer and Khong Arch Pathol Lab Med 2003;127:205-207

- Records from 1000 deliveries over 3 months
- Less than one-third of requisitions correctly and completely listed maternal indications
- Less than one-tenth of requisitions correctly and completely listed neonatal indications

How well are CAP guidelines followed?

- 53.8% had CAP “recommended” or “other” indications for examination
  - 17.8% had placental examination
- Indications with lowest examination rates
  - Meconium – 9.7%
  - Maternal fever – 13.7%
  - Suspected neonatal infection – 24.8%
  - IUGR – 26.7%
  - Maternal diabetes – 29.2%

Gross Examination

Three components

- Membranes
- Cord
- Disk

Gross Examination

- Placental weight
  - ***Do fresh***
  - Weigh ***after*** examining and removing cord, membranes and clot
  - Compare weight to standard chart
    - Low weight (< 10^{th} percentile)
      - Preeclampsia, growth retardation, maternal diseases, intrauterine infection, trisomy
    - Heavy weight (> 90^{th} percentile)
      - Anemia, maternal diabetes, infection (syphilis, toxo), hydrops fetalis

Gross Examination

Fetal membranes

- Completeness
- Point of rupture
  - Shortest distance from end of membranes to disk
  - Tells where in uterus placenta implanted
- Type of insertion
  - Circummarginate
  - Circumvallate

Gross Examination

Fetal Membranes

- Color – meconium, hemosiderin
- Opacity – chorioamnionitis
- Nodules – squamous metaplasia, amnion nodosum
- Bands – amnionic band syndrome
- Retromembranous hematoma

Gross Examination

Umbilical cord

- Length, diameter
- Number of vessels – normal is three
  - ***Don't take section at insertion site***
- Type of insertion
  - Marginal
  - Velamentous – look for lacerations, thrombi
    - Take section of intramembranous vessels

Gross Examination

Focal cord abnormalities

- Knots – ***photograph***, loose vs. tight, describe cord color and diameter on either side, sample vessels on either side for thrombi
- Stricture
- Excess twisting – measure # of twists/10 cm and compare to a standard chart
- Hematoma
- Edema

Gross Examination

Fetal surface of placental disk

- Color – meconium, chorioamnionitis
- Bands – amnionic bands
- Nodules – squamous metaplasia, Amnion nodosum
- Clot – subamnionic hematoma

Gross Examination

Fetal surface of placental disk

- Chorionic vessels
  - Thrombi
  - Lacerations
  - Calcification – old thrombi, toxoplasmosis

Gross Examination

Placental Disk – maternal surface

- Assess completeness
- Measure in three dimensions
- Slice disk at 1 cm intervals
  - Examine and palpate each slice
- Focal lesions
  - Size – measure in 3 dimensions
  - Location – central or peripheral
  - Shape – well circumscribed, fuzzy borders
  - Color - red (recent), white (older)
  - *Percent of placental parenchyma it occupies*

Gross Examination

Sections

- One with two sections of cord and one of membrane roll
- Two of central placental tissue
  - fetal surface
  - maternal surface
- Additional sections if abnormalities

Quality of Pathology Reports

Khong and Gordijin Ped Devel Pathol 2002;6:54-58

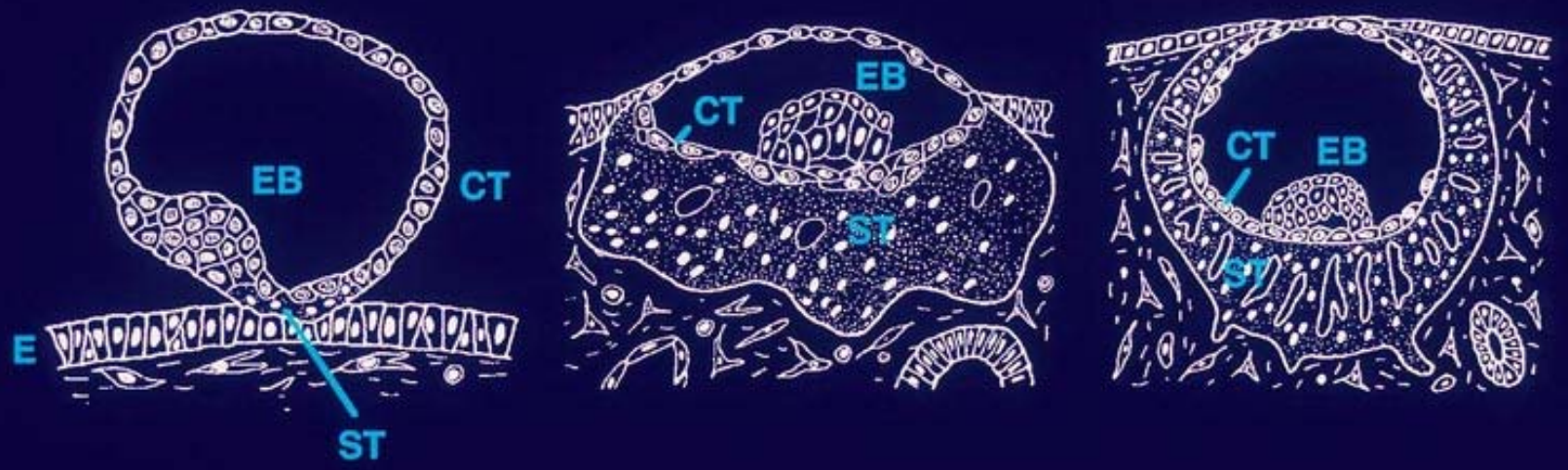
- Scored 218 placental reports for gross, histologic features and commentary on findings related to clinical history
- 33% of singleton and 41% of multiple gestations scored < 75%
- Poorly reported features – completeness of membranes, zygosity in twins, birth order of twins, commentary on gross or histologic findings

Reliability of Diagnoses

Discrepancies occur in about 40% of cases

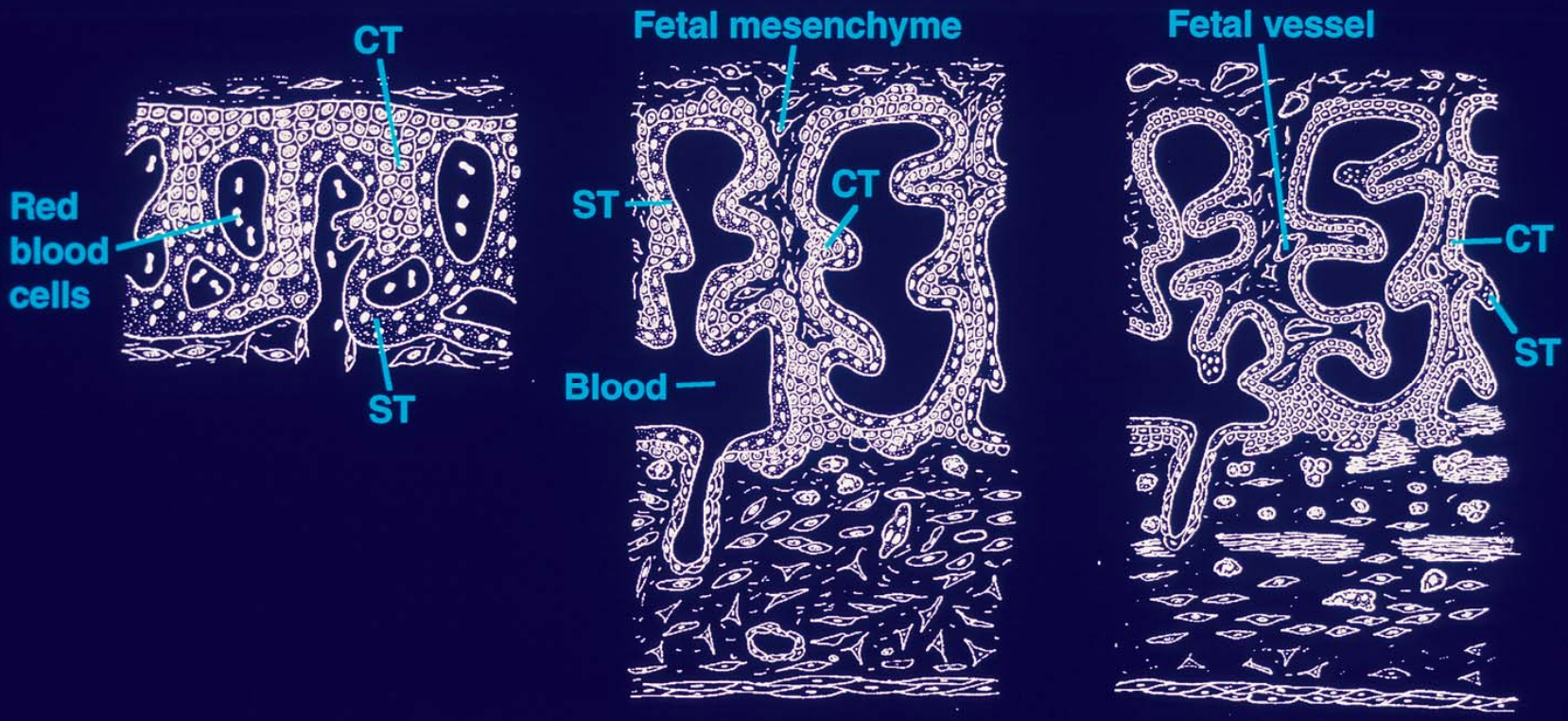
- Nearly all represent underdiagnosis
- Most commonly underdiagnosed conditions:
  - Hemorrhagic endovasculitis
  - Fetal thrombotic vasculopathy
  - Massive perivillous fibrin deposition
  - Maternal floor infarct
  - Retroplacental hematoma
  - Intervillous thrombohematoma
  - Acute atherosis

Early Villous Development



after: Benirschke & Kaufman *Pathology of the Human Placenta*

Early Villous Development



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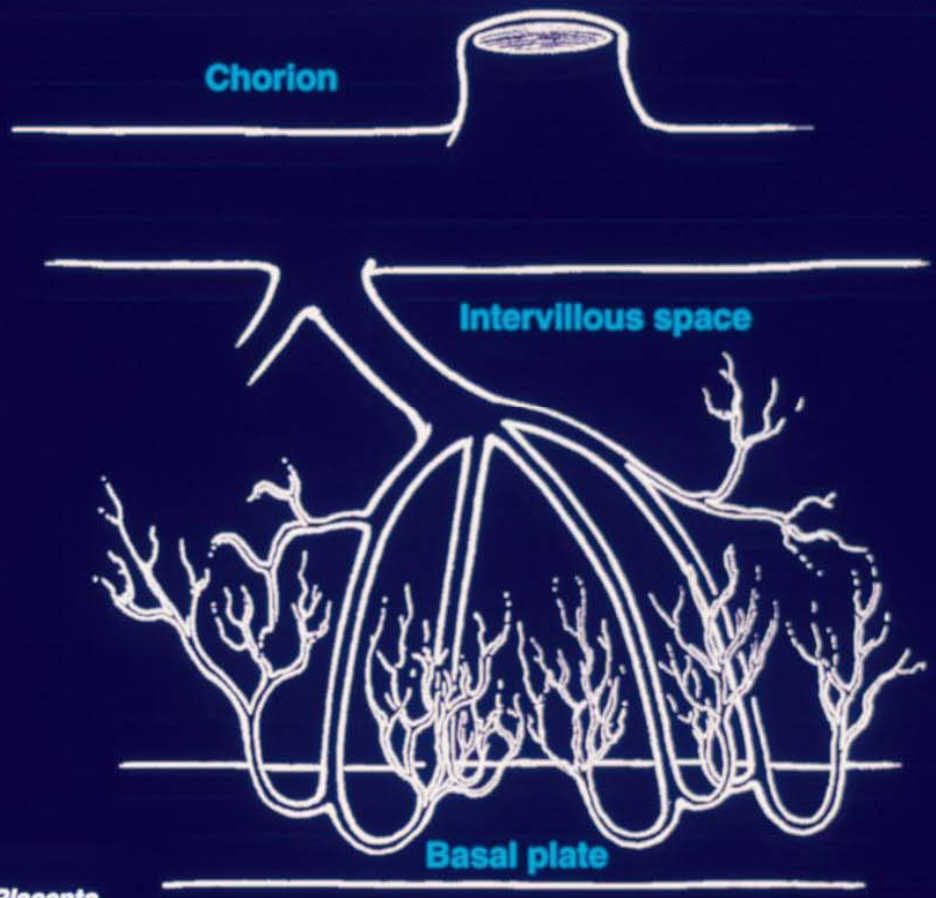
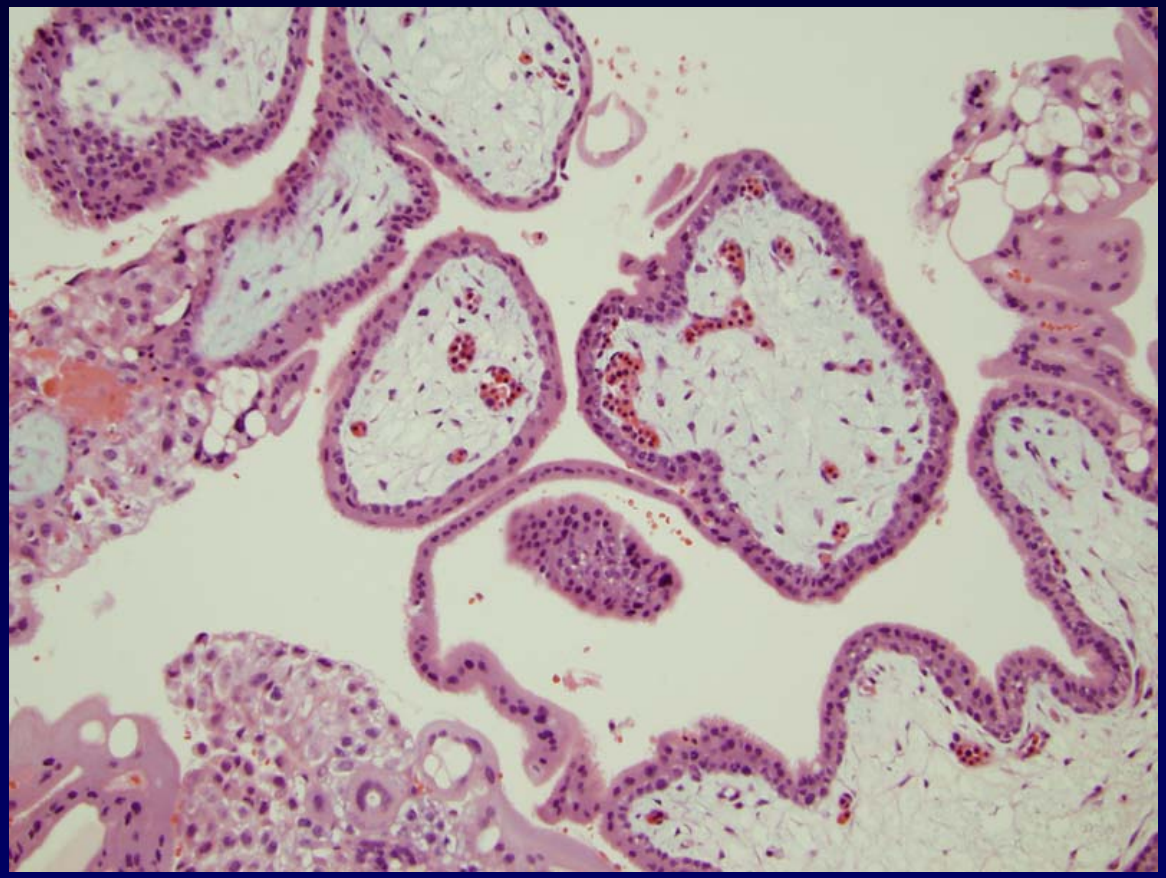
Villous Development



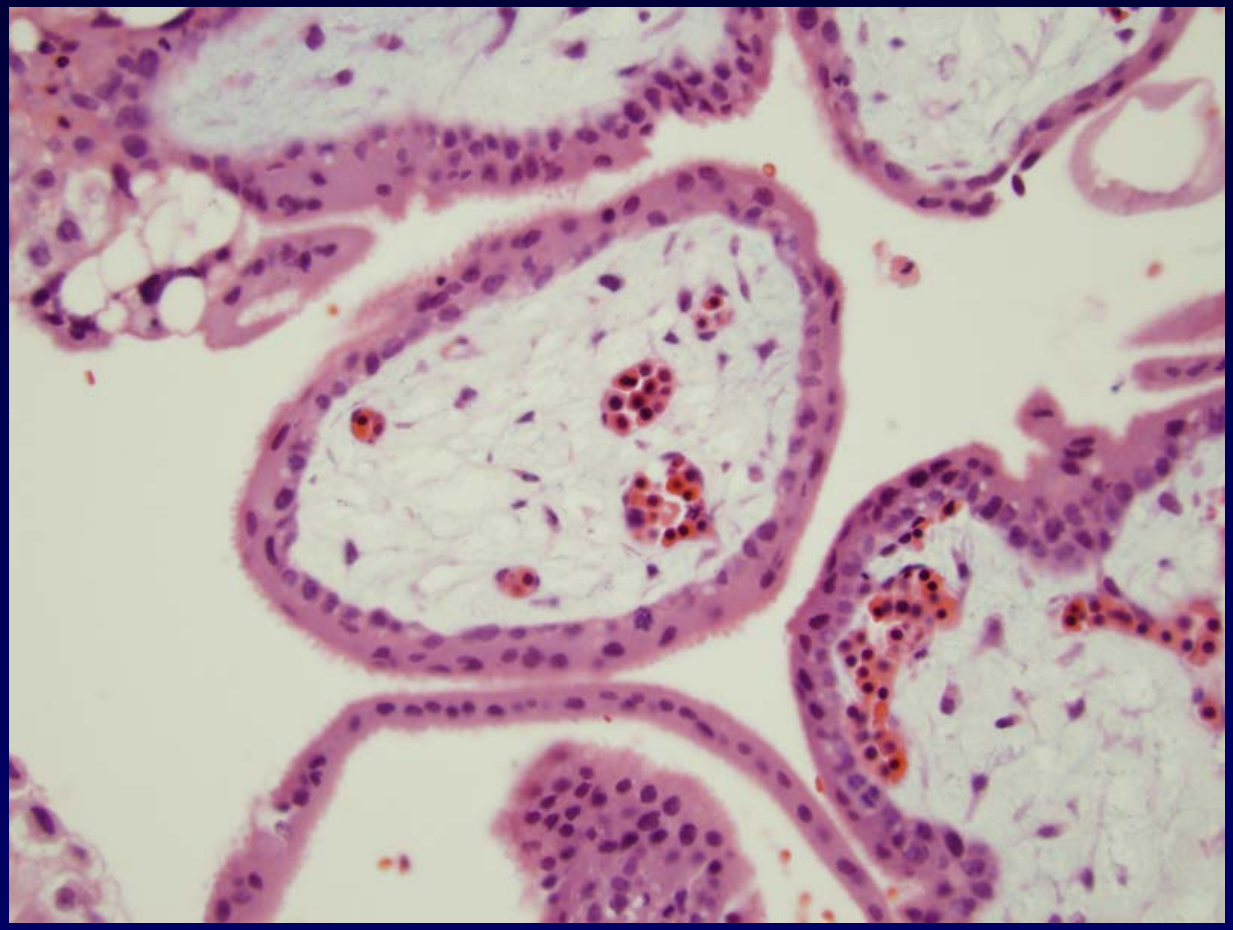
After: Fox H. *Pathology of the Placenta*

Normal First Trimester Villi



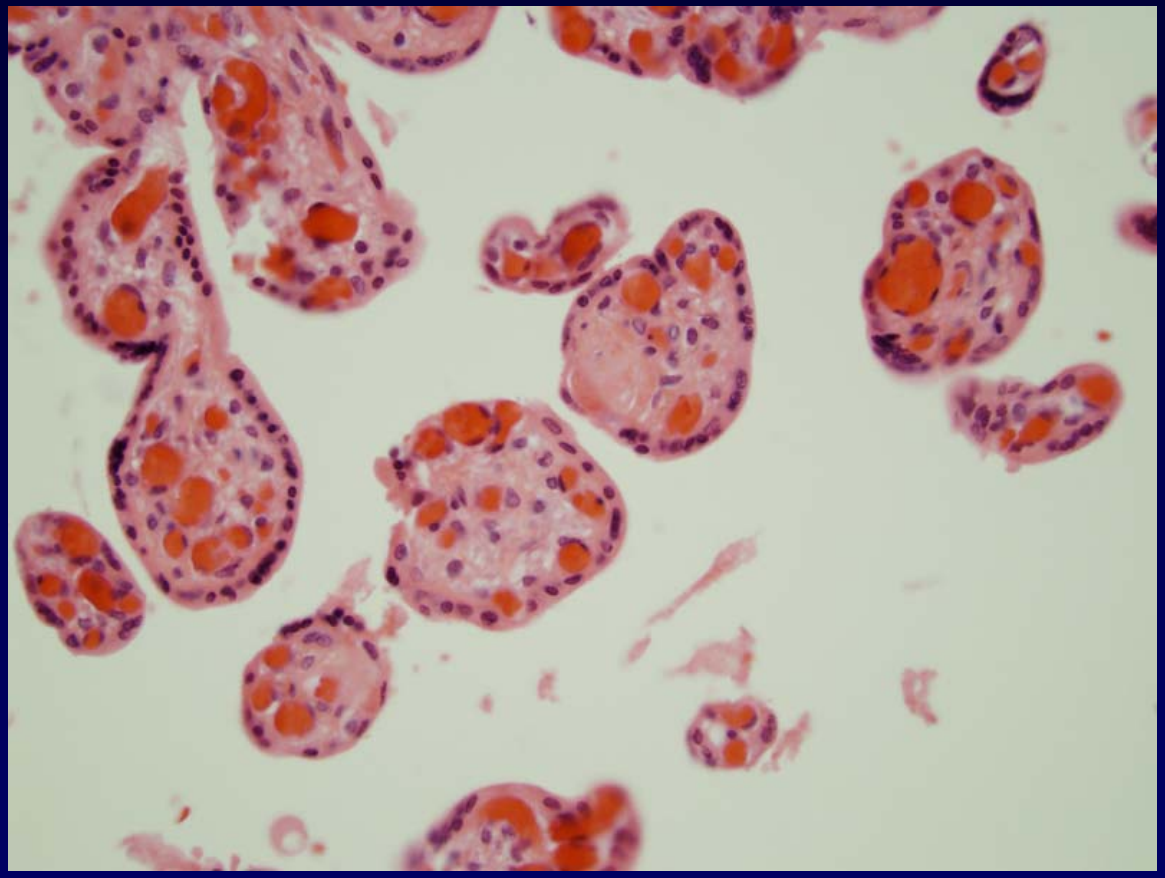
- stroma makes up most of area
- vessels are randomly distributed

Normal First Trimester Villi

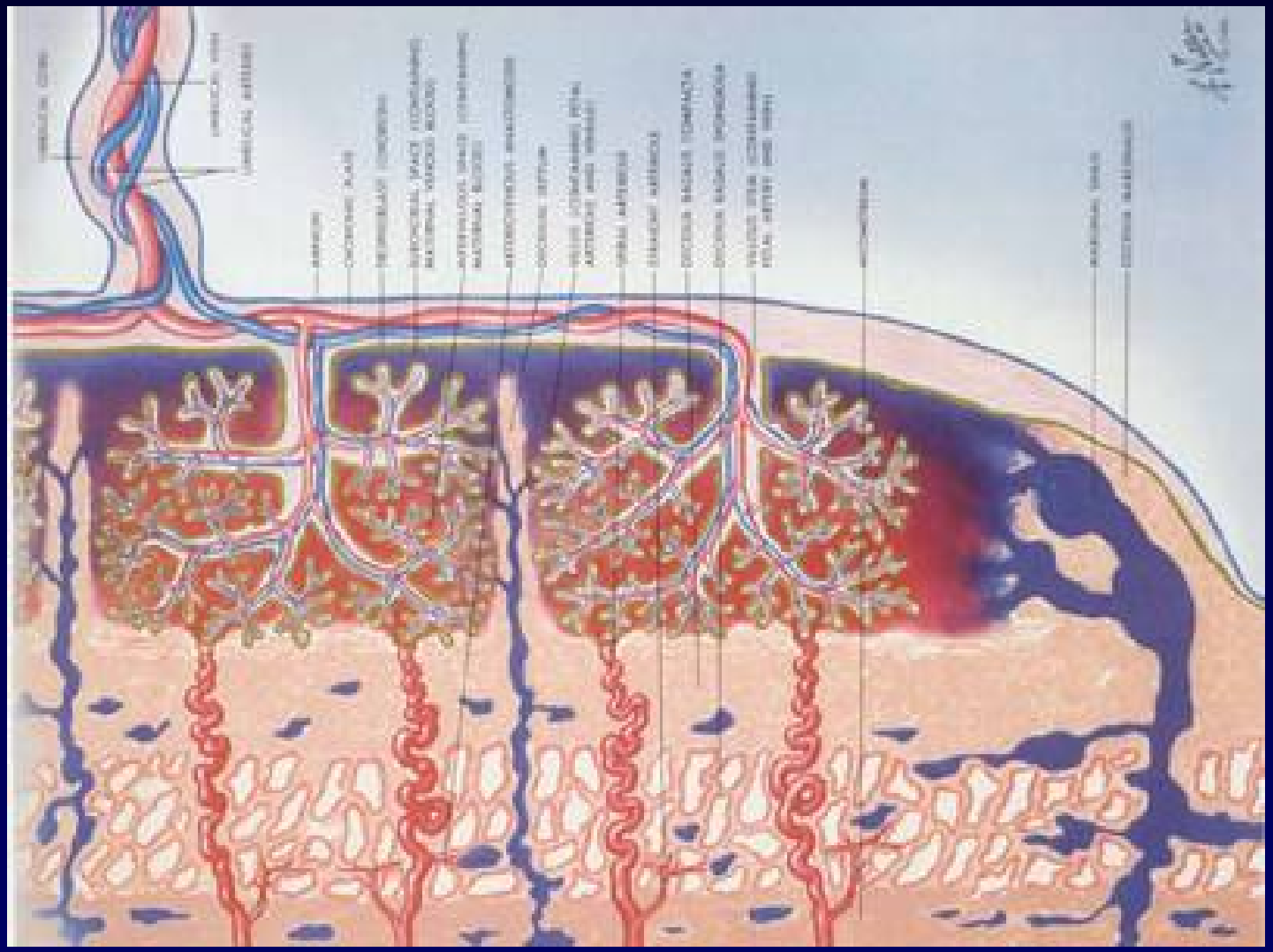


distinct cytotrophoblastic layer

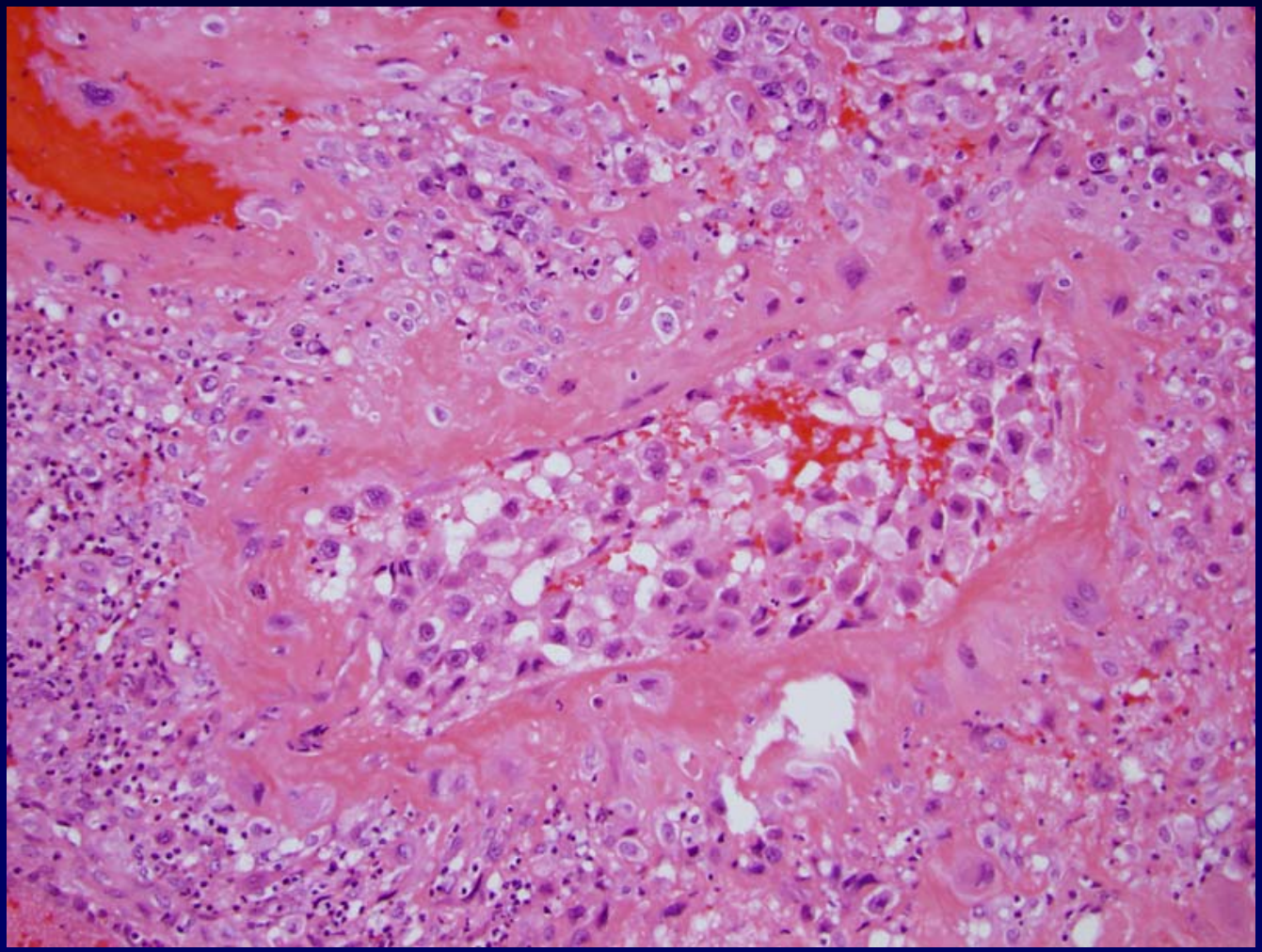
Third Trimester Villi



- cross sectional area is mostly vessels
- vessels are located in the periphery

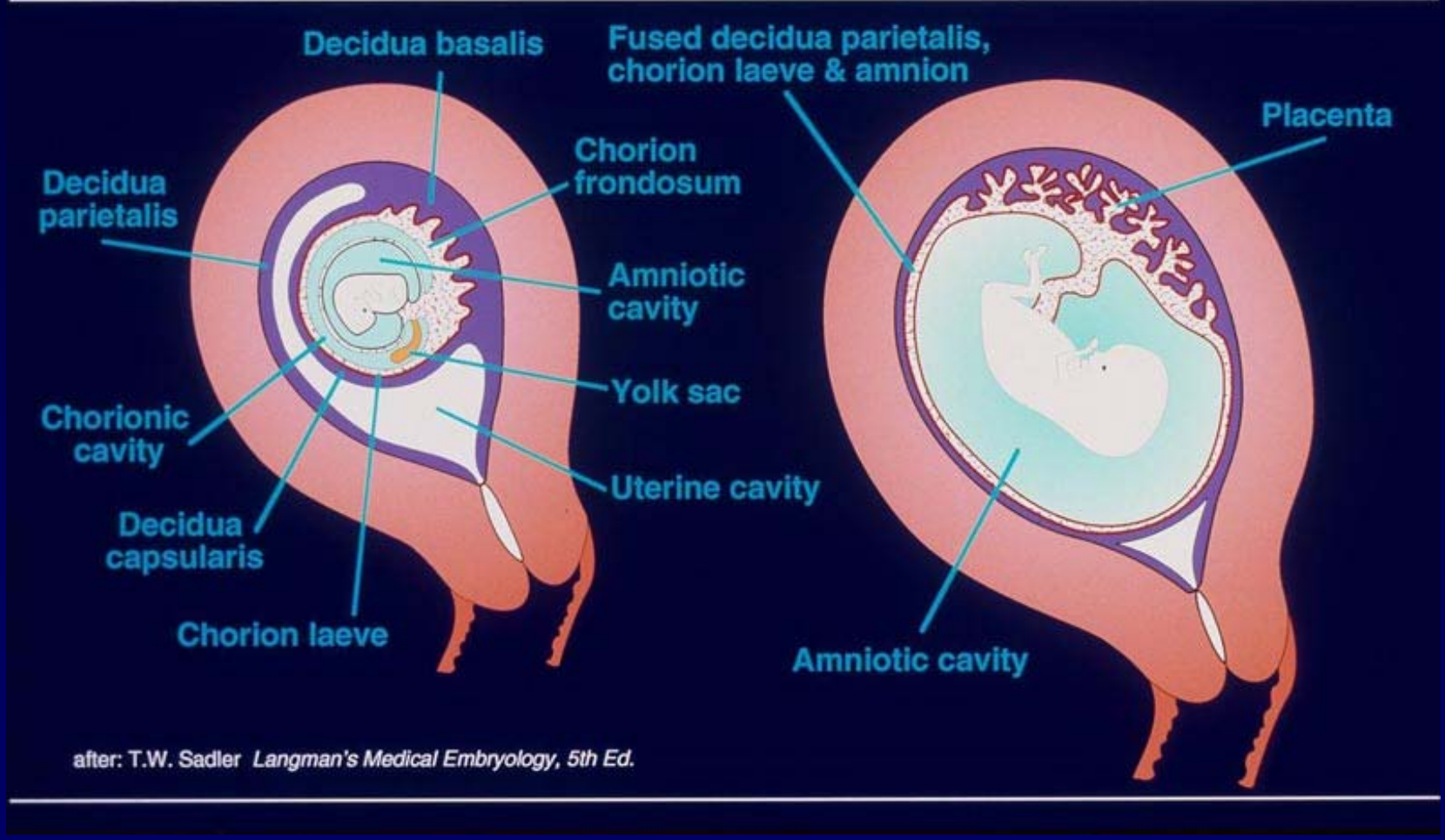


Implantation Site Vessels

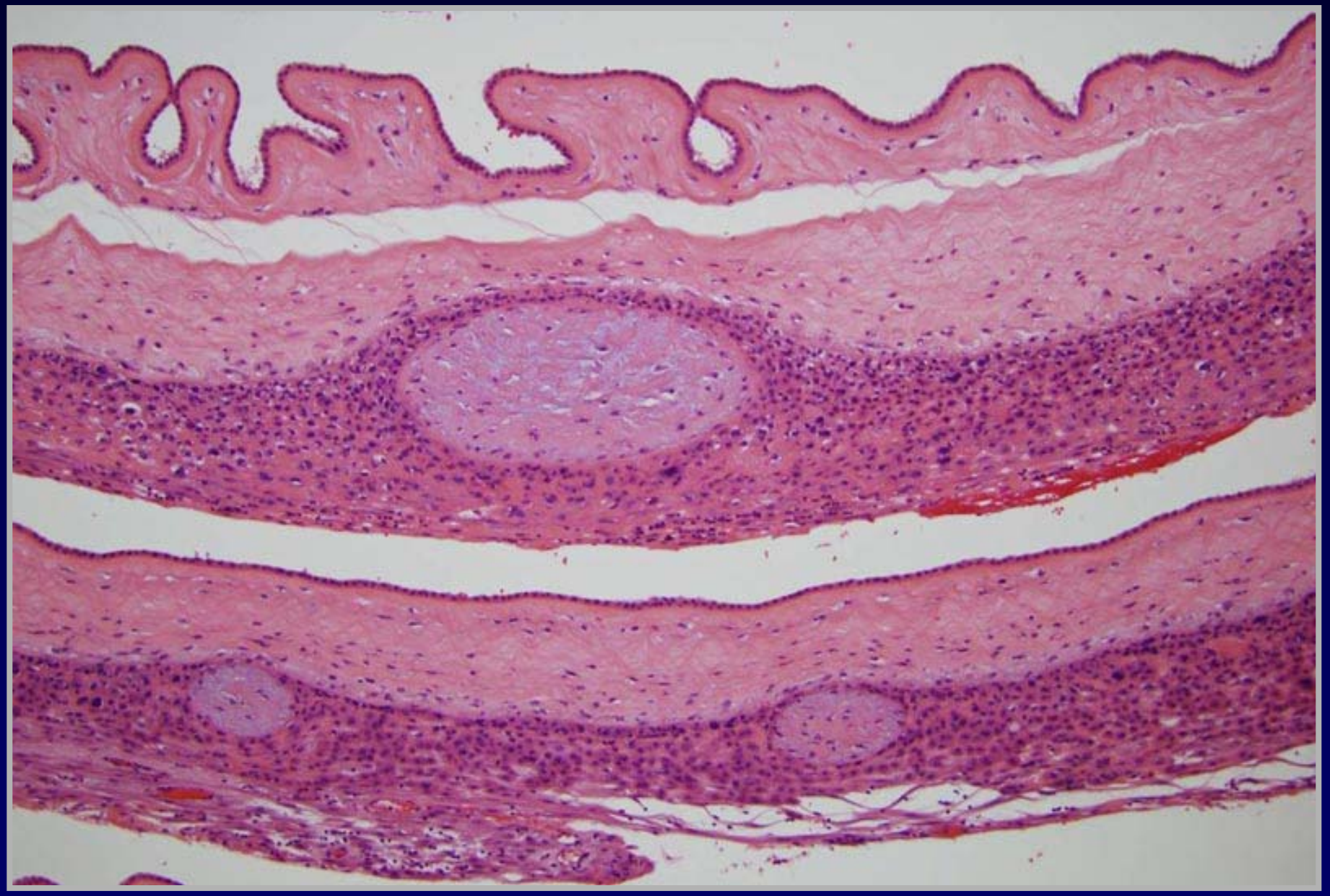


Prominent endovascular trophoblast

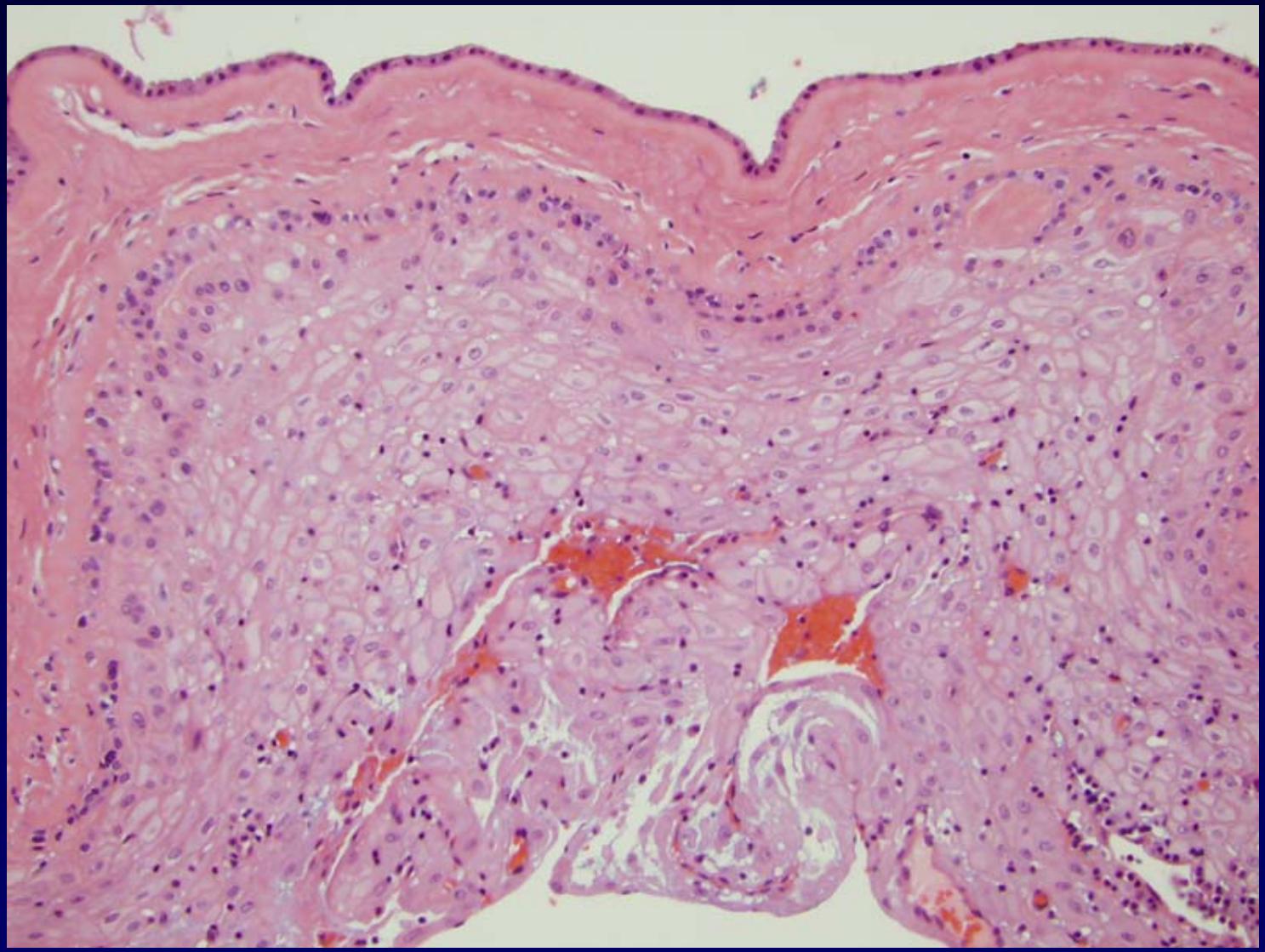
Development of Fetal Membranes



after: T.W. Sadler *Langman's Medical Embryology, 5th Ed.*



Normal Membranes



Circulatory Disorders

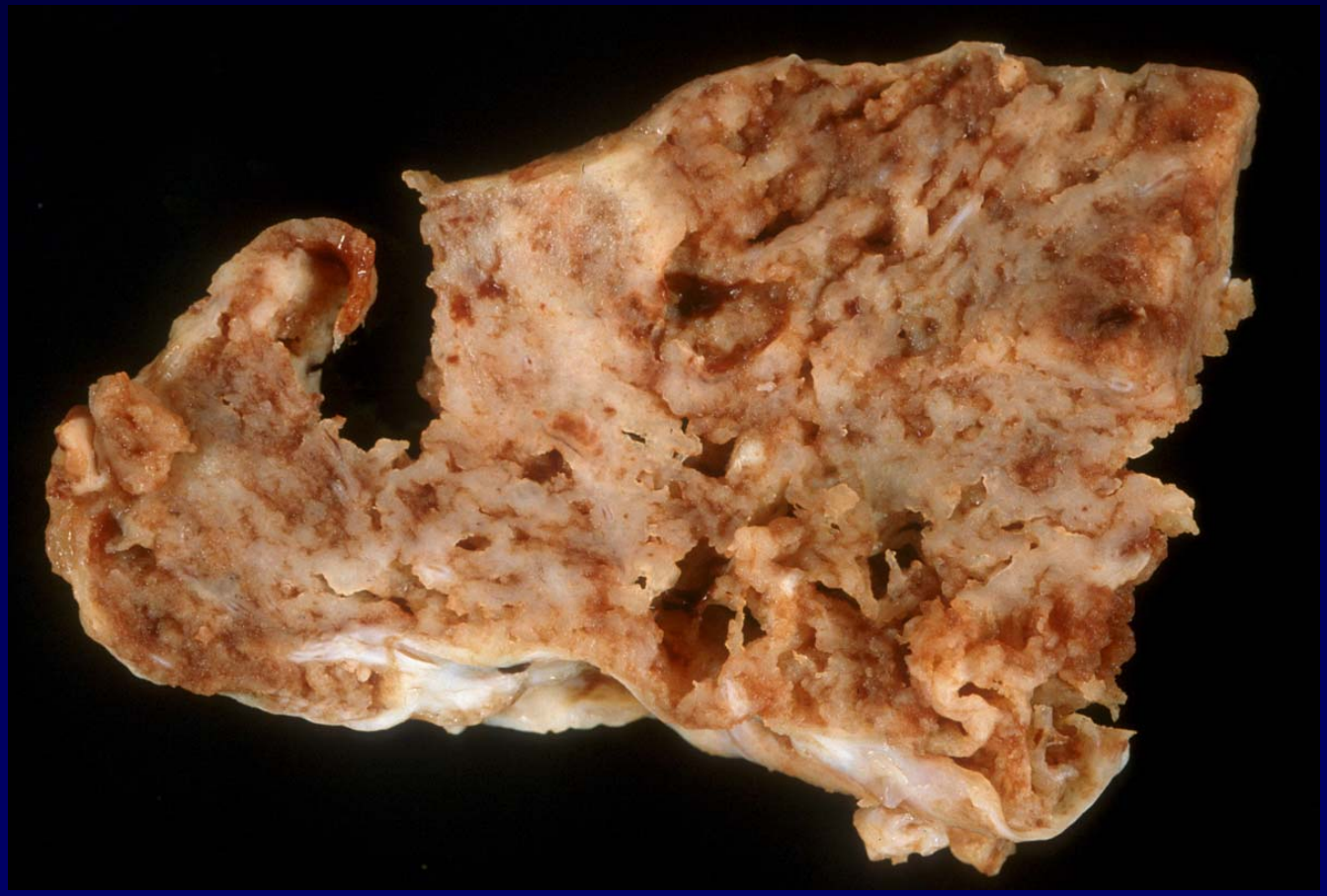
Disorders of the maternal circulation

- Massive perivillous fibrin deposition
- Maternal floor infarct
- Subchorionic fibrin deposition
- Infarcts
- Retroplacental hematoma
- Marginal hematoma
- Intervillous thrombohematoma
- Subamniotic hematoma
- Massive subchorial thrombosis (Breus' mole)

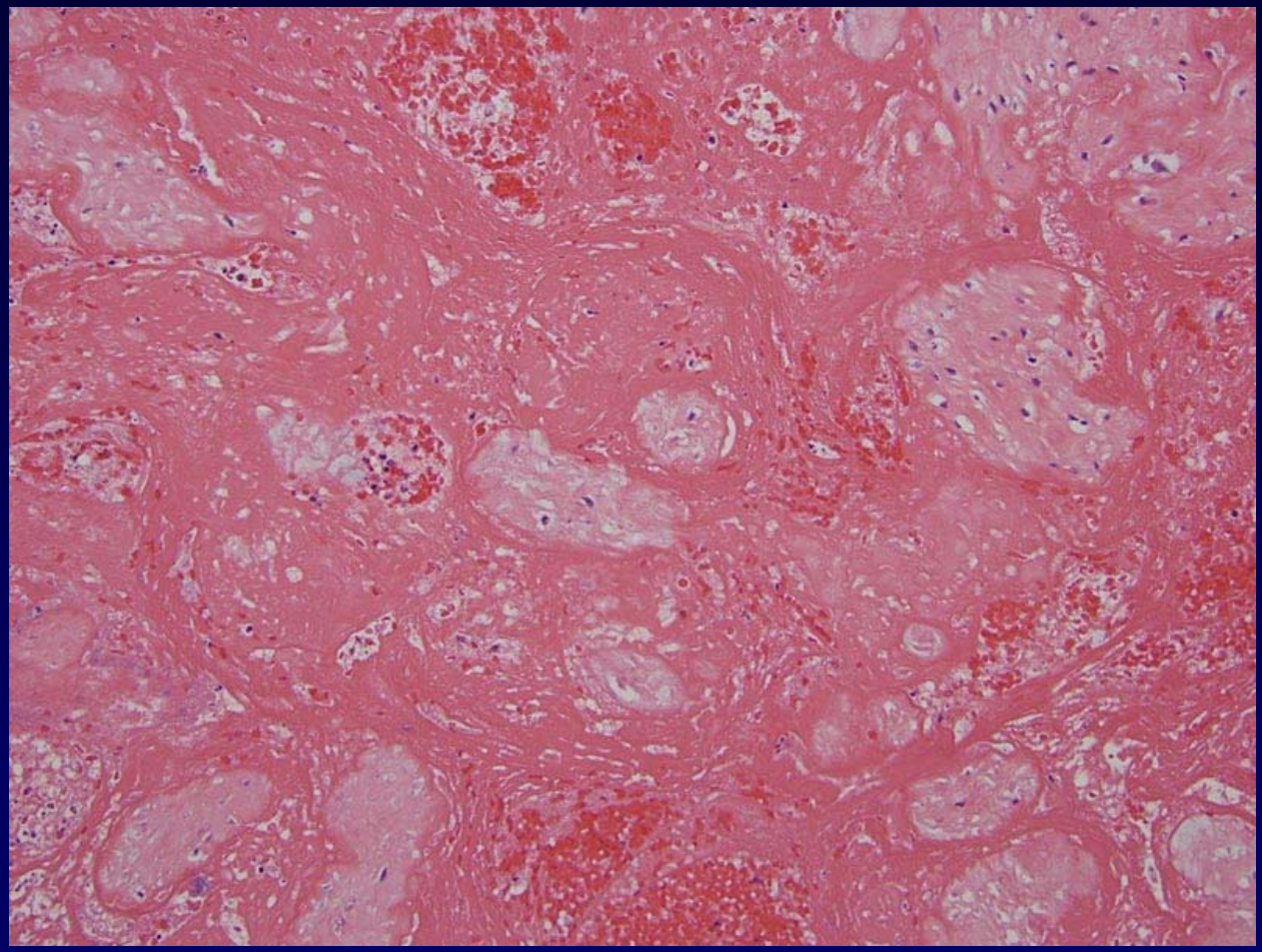
Case 1

The patient is a 25 year old G7P2042 woman at 29 and 6/7 weeks gestation. The fetus had severe intrauterine growth restriction and was estimated at less than the 1st percentile for weight. The placenta was small and firm at delivery.

Massive Perivillous Fibrin Deposition

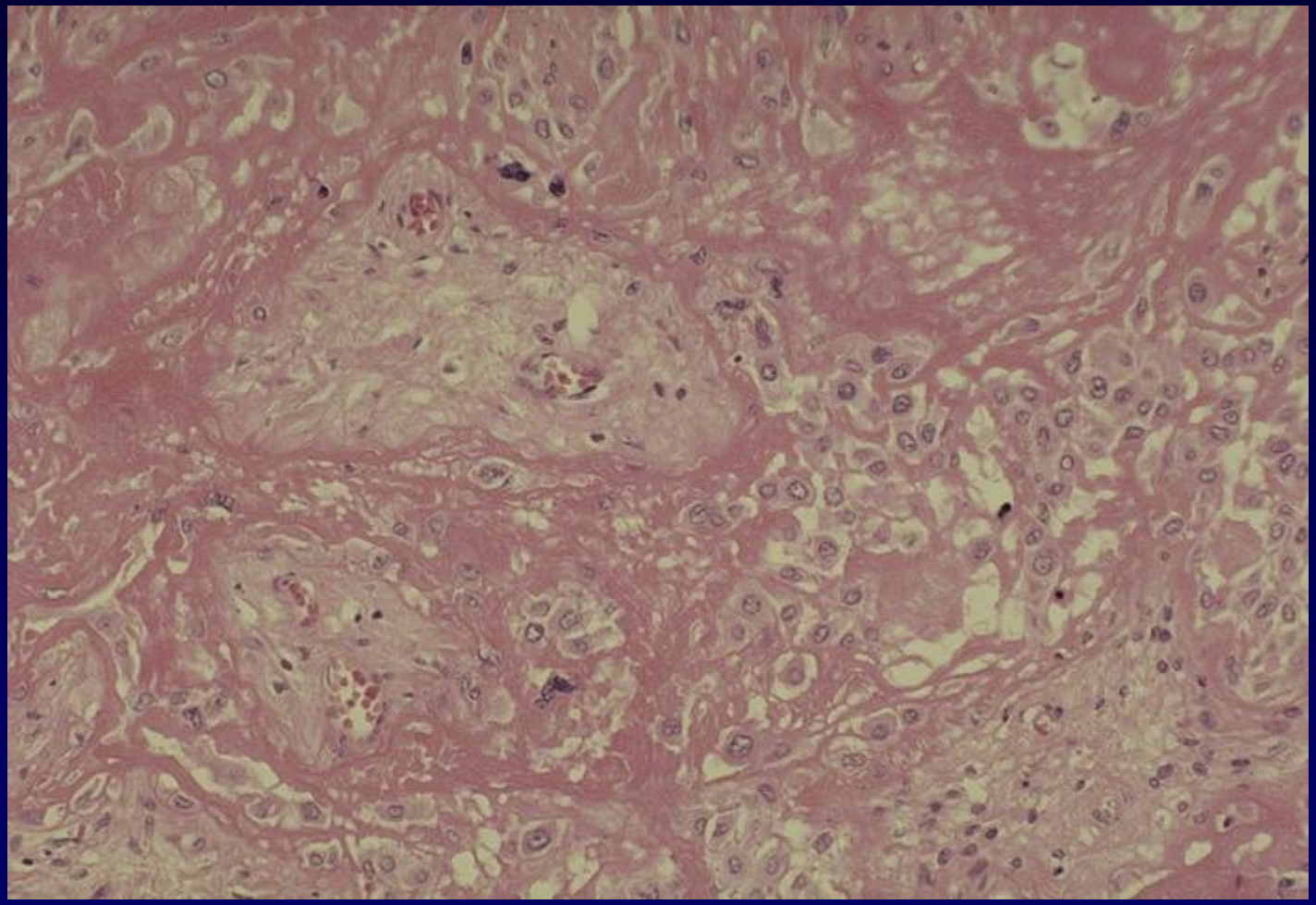


Perivillous Fibrin Deposition



Expansion of intervillous space

Perivillous Fibrin Deposition

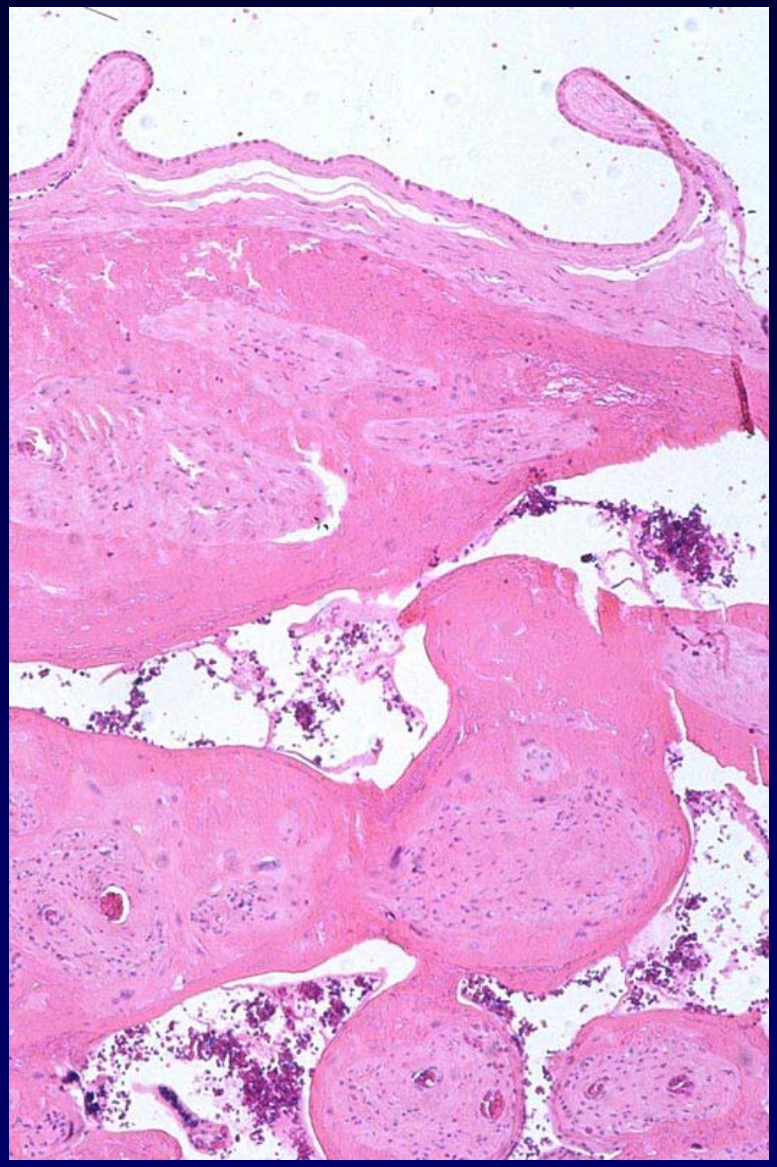


Cytotrophoblast proliferation

Perivillous Fibrin

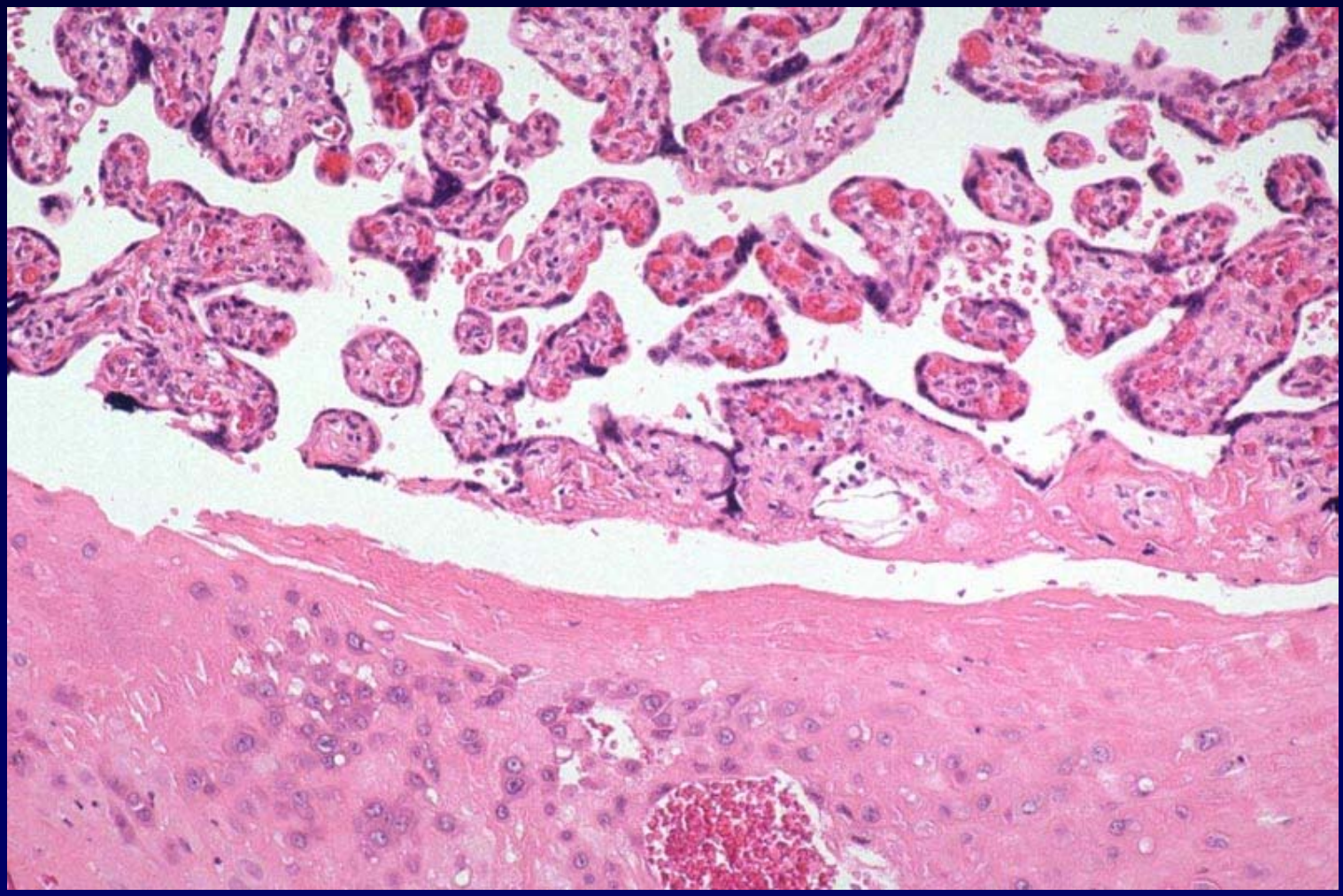
- See some fibrin in most placentas
- Grossly visible fibrin in 22%
  - Underneath chorionic plate
  - Around stem villi
  - Just above basal plate

Normal Fibrin Deposition



- Beneath chorionic plate
- Around stem villi

Normal Fibrin Deposition



Above basal plate

Perivillous Fibrin

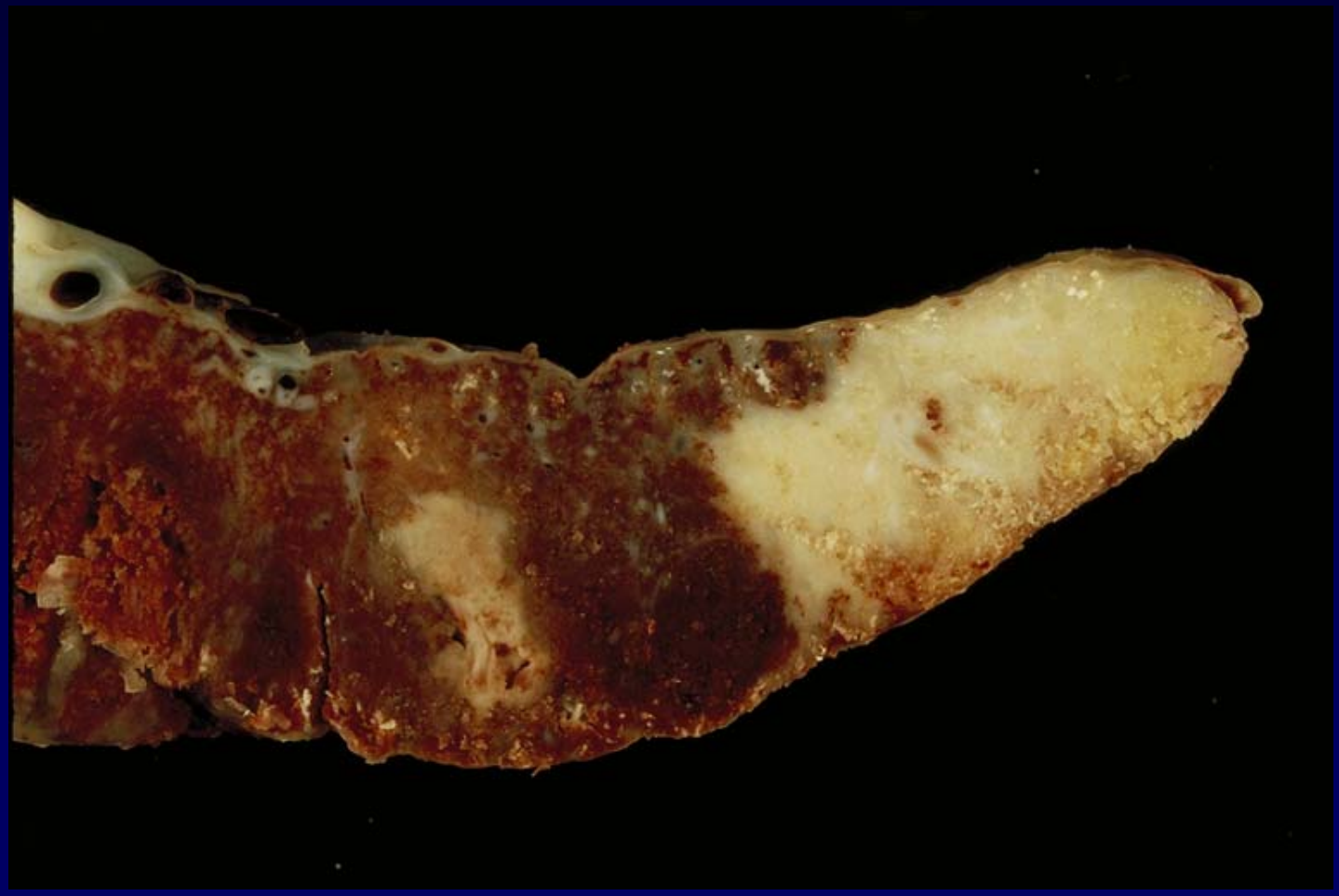
- See some fibrin in most placentas
- Grossly visible fibrin in 22%
  - Underneath chorionic plate
  - Around stem villi
  - Just above basal plate
- See less in preeclampsia (13%)
- See less in preterm (6%)

Fibrin Deposition

Gross

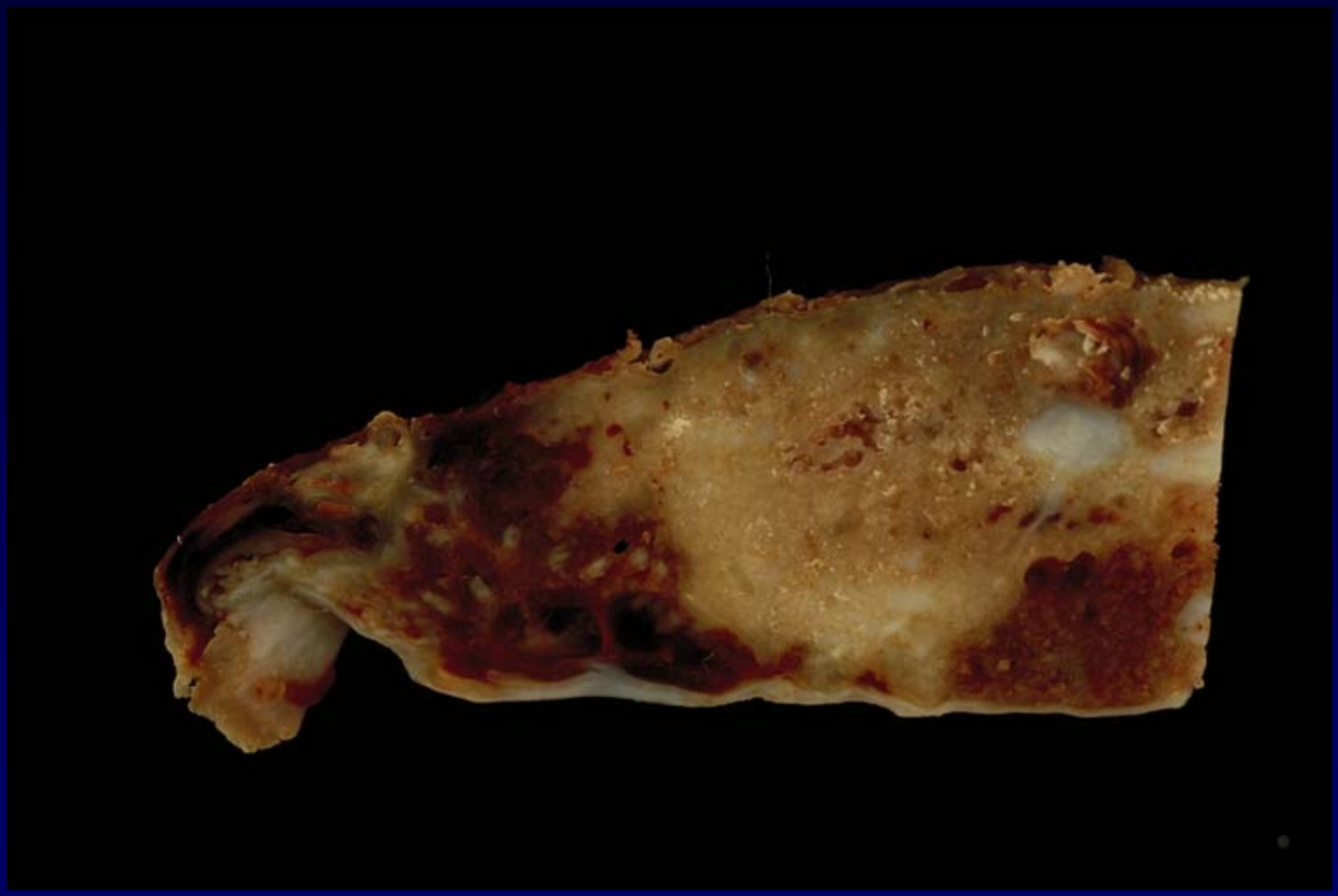
- Firm, tan, yellow or white
- Fuzzy border
  - Interspersed red villous tissue
  - Not as well circumscribed as infarct
- Often in periphery

Perivillous Fibrin Deposition



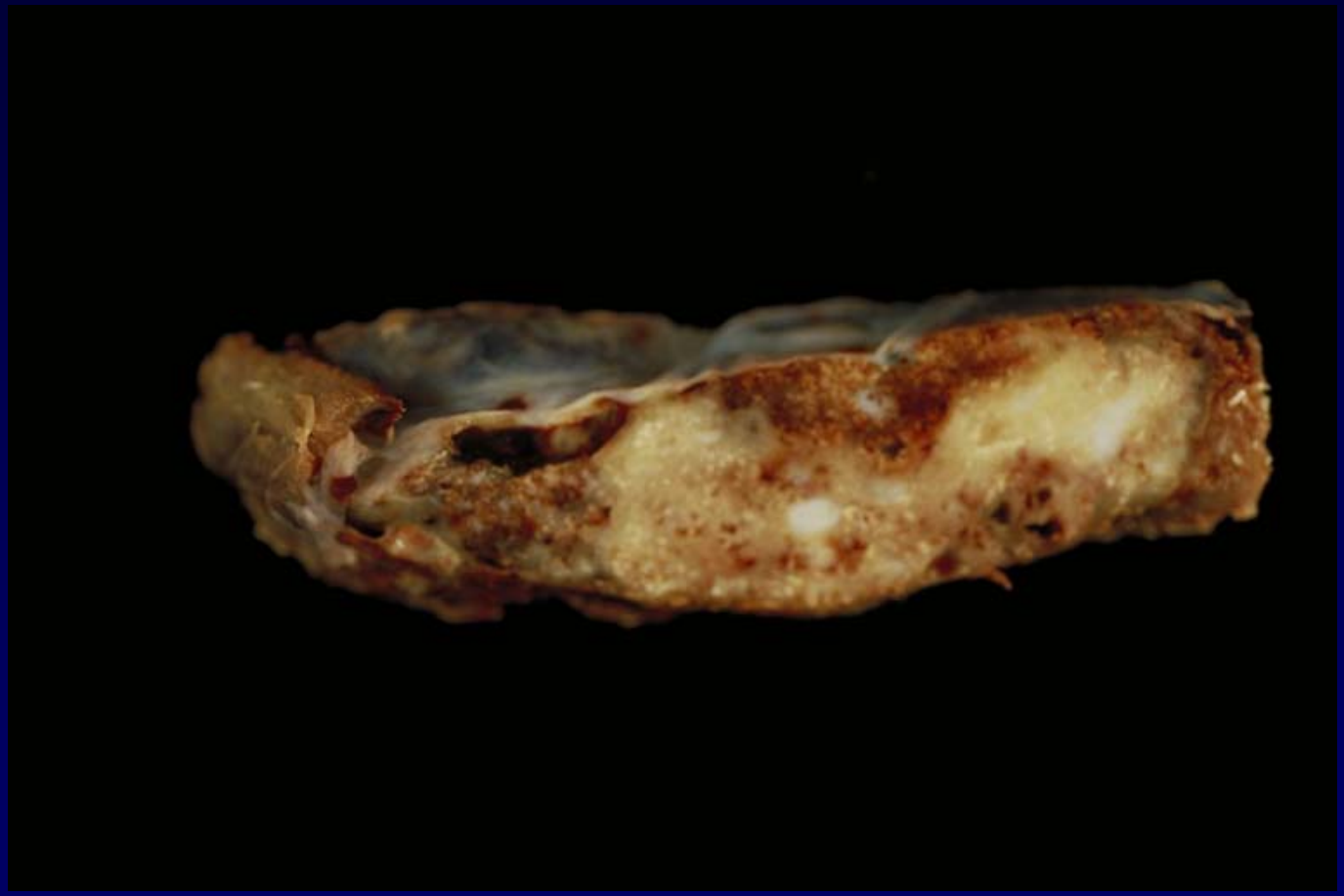
Not as well circumscribed as infarcts

Perivillous Fibrin Deposition



Not well circumscribed, fuzzy borders

Perivillous Fibrin Deposition



Surrounds normal, red villous tissue

Perivillous Fibrin Deposition

Clinically significant if:

- Entraps 20% of terminal villi
- Central-basal location

Clinical significance

- Intrauterine growth retardation
- Low placental weight
- Fetal death in utero
- Periventricular leukomalacia if preterm

Perivillous Fibrin Deposition

Katzman and Genest

- Transmural massive fibrin deposition (MFD)
  - Extends from fetal to maternal surface
  - Entraps > 50% of villi on at least one slide
  - Rare - 0.28 to 0.5% of examined placentas

Pediatr Dev Pathol 2002;5:159-164

Perivillous Fibrin Deposition

Katzman and Genest

- 31% of infants had IUGR
- 14% had MFD or maternal floor infarct in other 2nd or 3rd trimester pregnancies
- 50% had MFD or maternal floor infarct in other 1st trimester pregnancies

Pediatr Dev Pathol 2002;5:159-164

Perivillous Fibrin

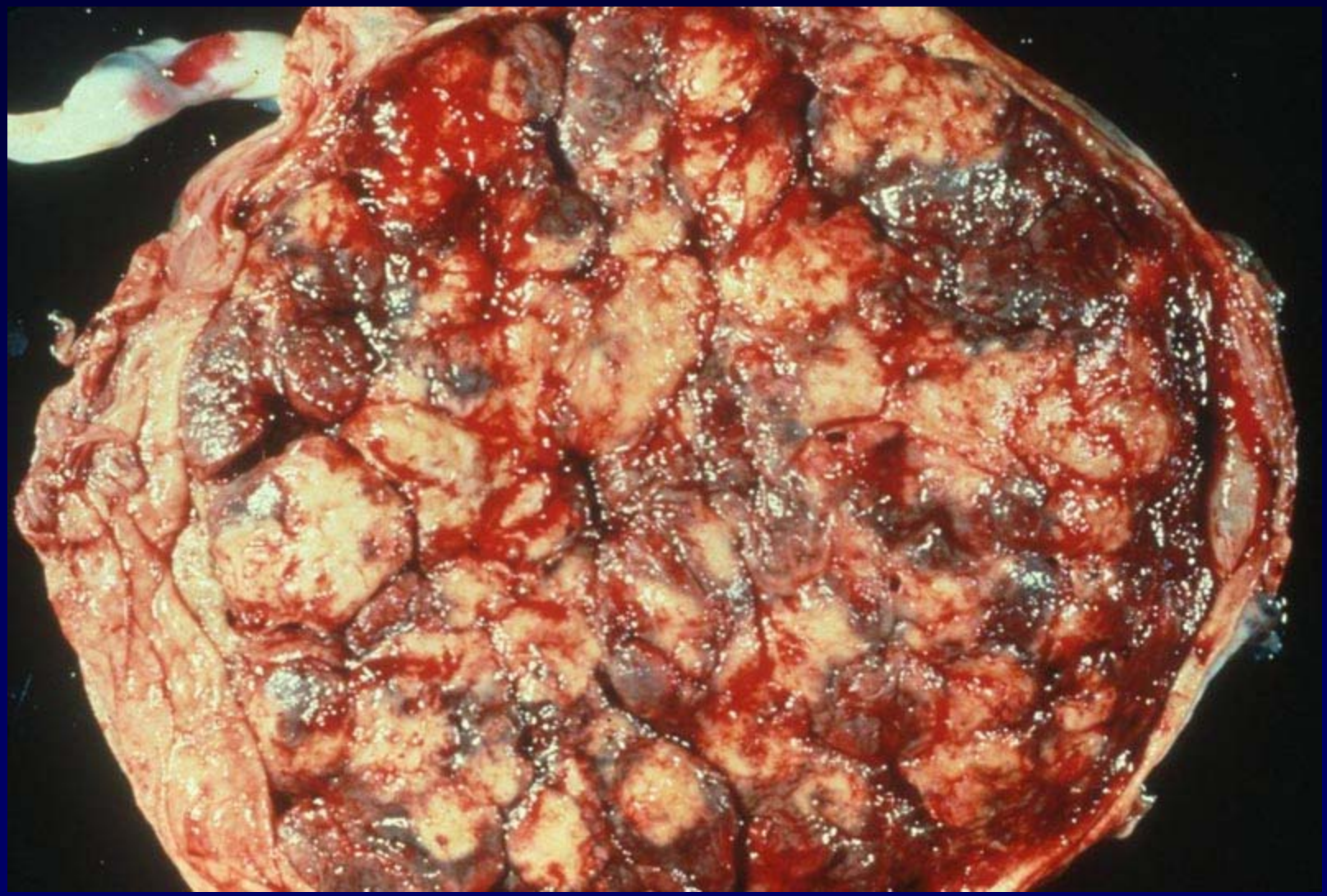
- Pathogenesis is unclear
- Likely related to stasis and thrombosis of maternal blood

Perivillous Fibrin

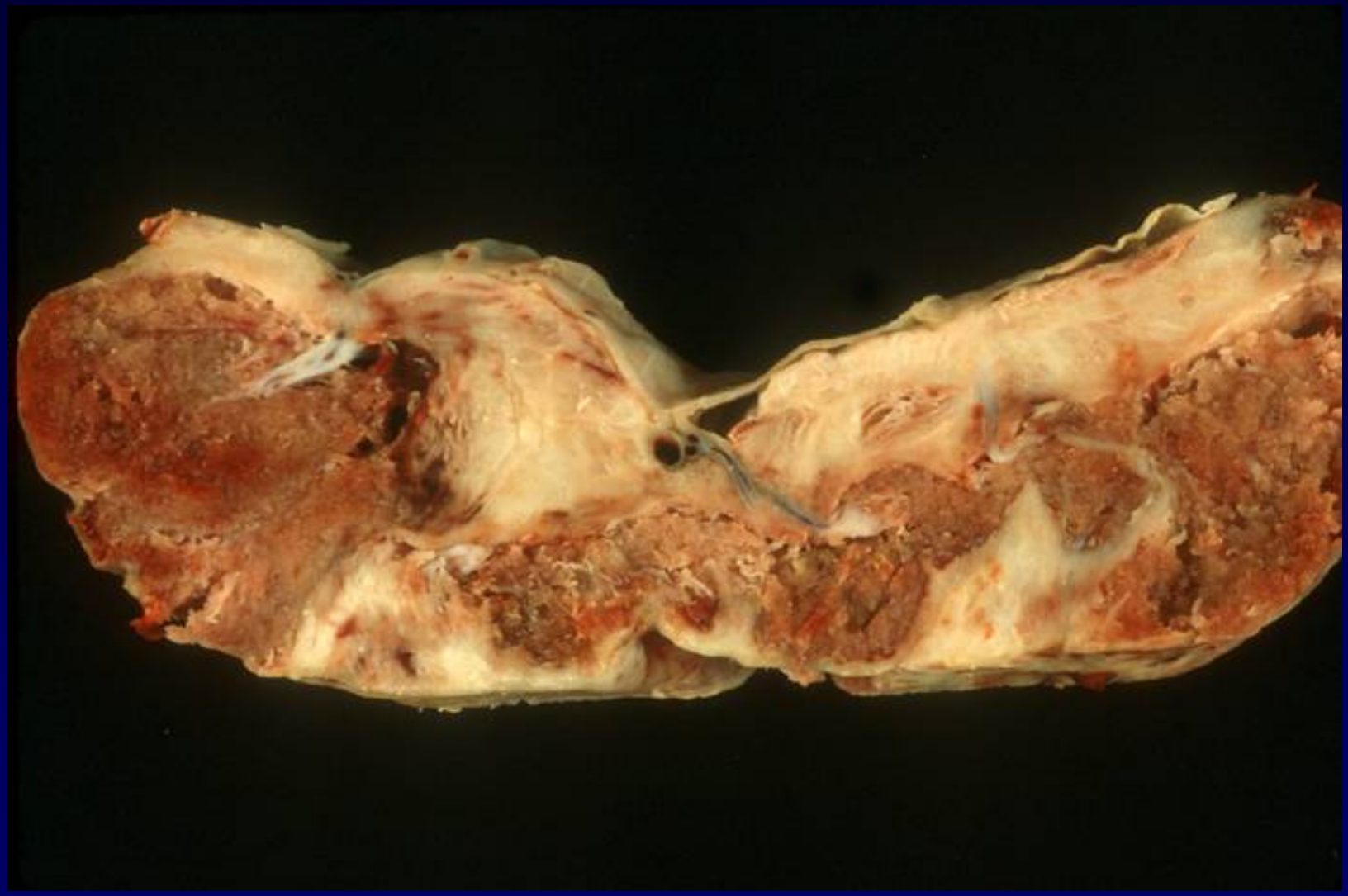
- Massive perivillous fibrin in small for gestational age (SGA) and prior SGA
- Preeclampsia, collagen vascular diseases, coagulopathy
- Aspirin, dipyridamole prevents perivillous fibrin and SGA

Fuke Y et al Gyn Obstet Invest 38:5-9, 1994

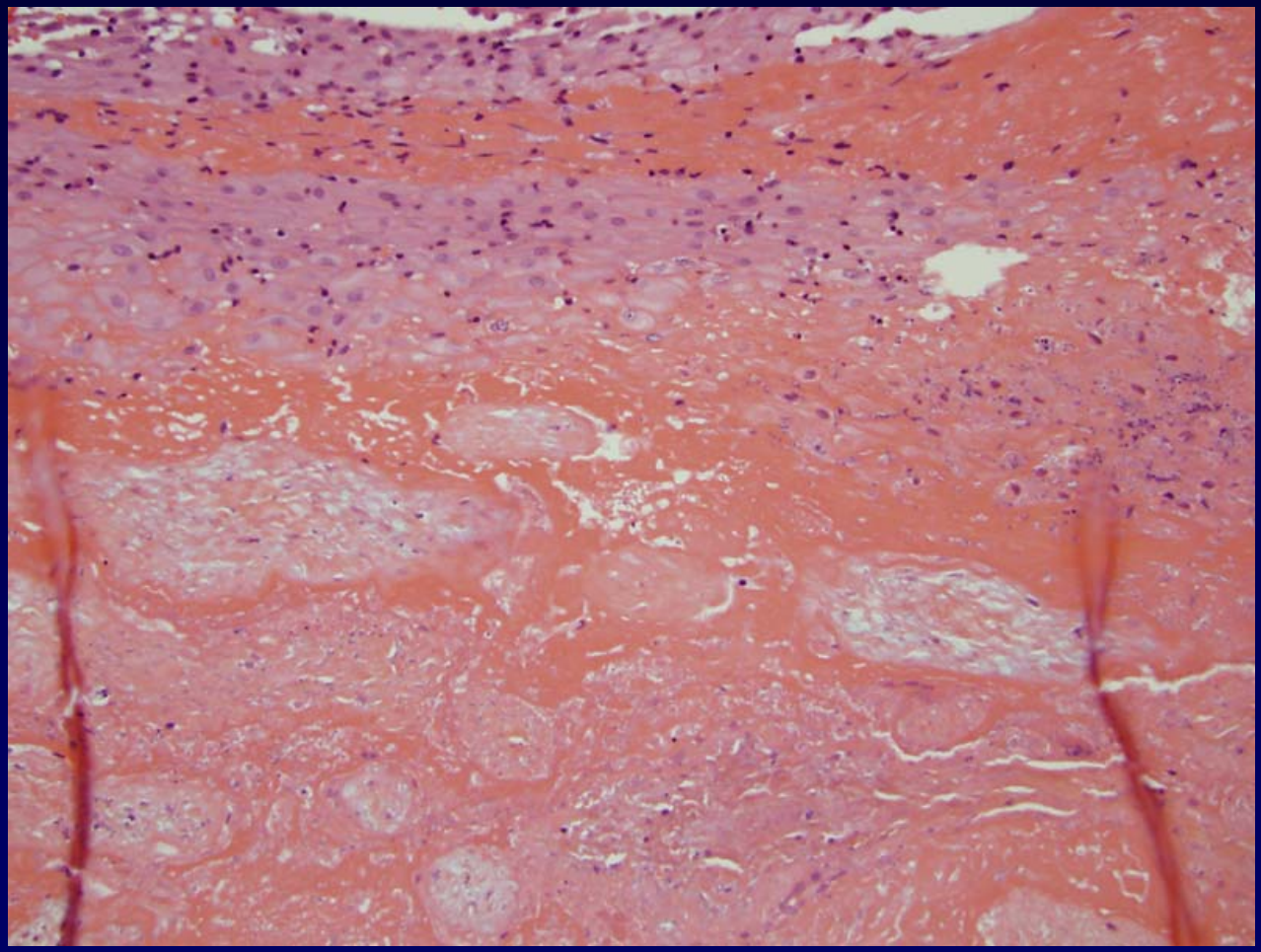
Maternal Floor Infarct



Maternal Floor Infarct



Maternal Floor Infarct



Maternal Floor Infarct

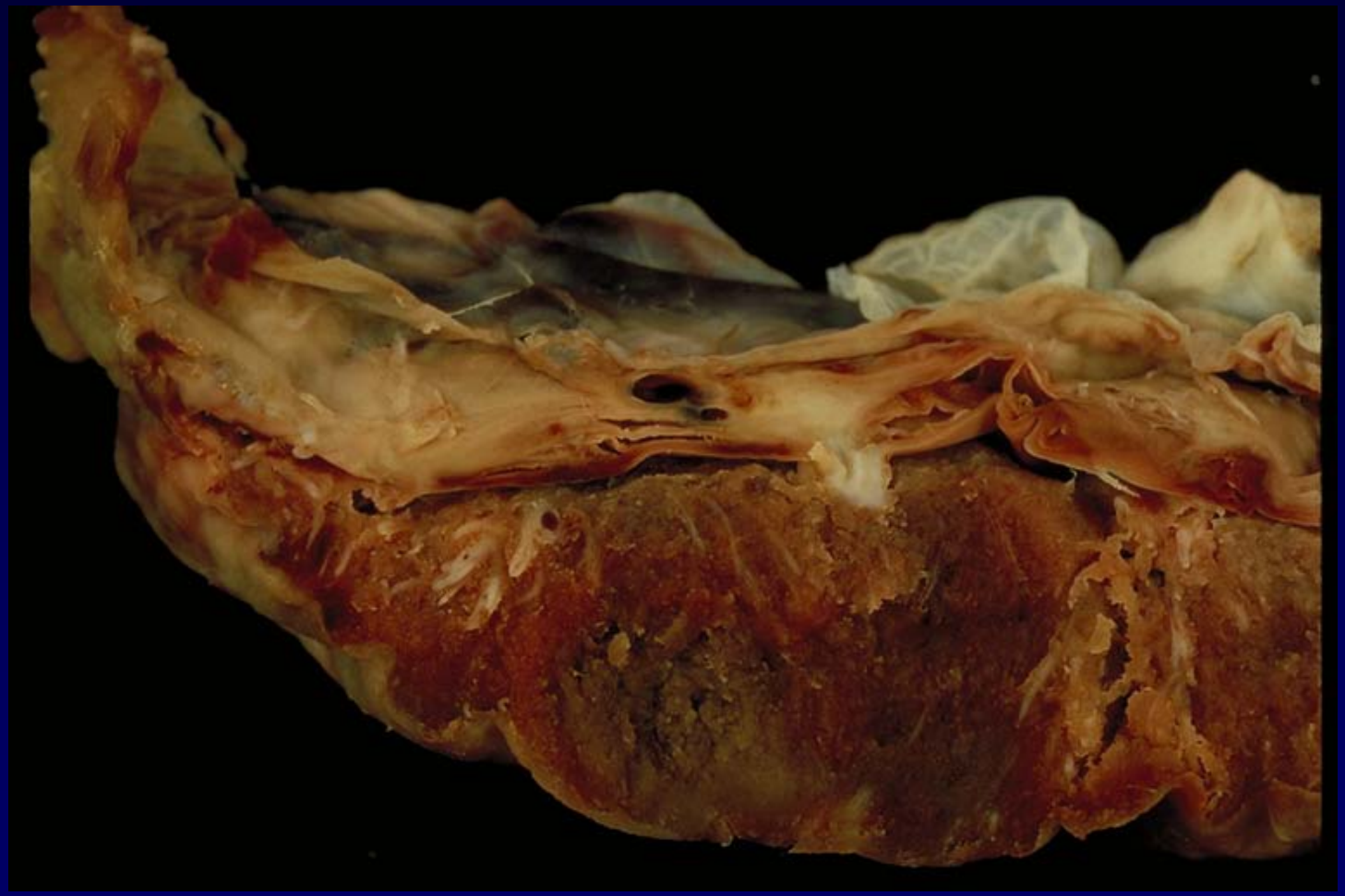
- Infarct is a misnomer - fibrinoid deposition
- Fibrinoid involves decidua basalis
- Encases adjacent villi
- Katzman and Genest definition
  - Basal villi of entire maternal floor be encased by fibrinoid at least 3 mm thick on at least one slide

Pediatr Dev Pathol 2002;5:159-164

Maternal Floor Infarct

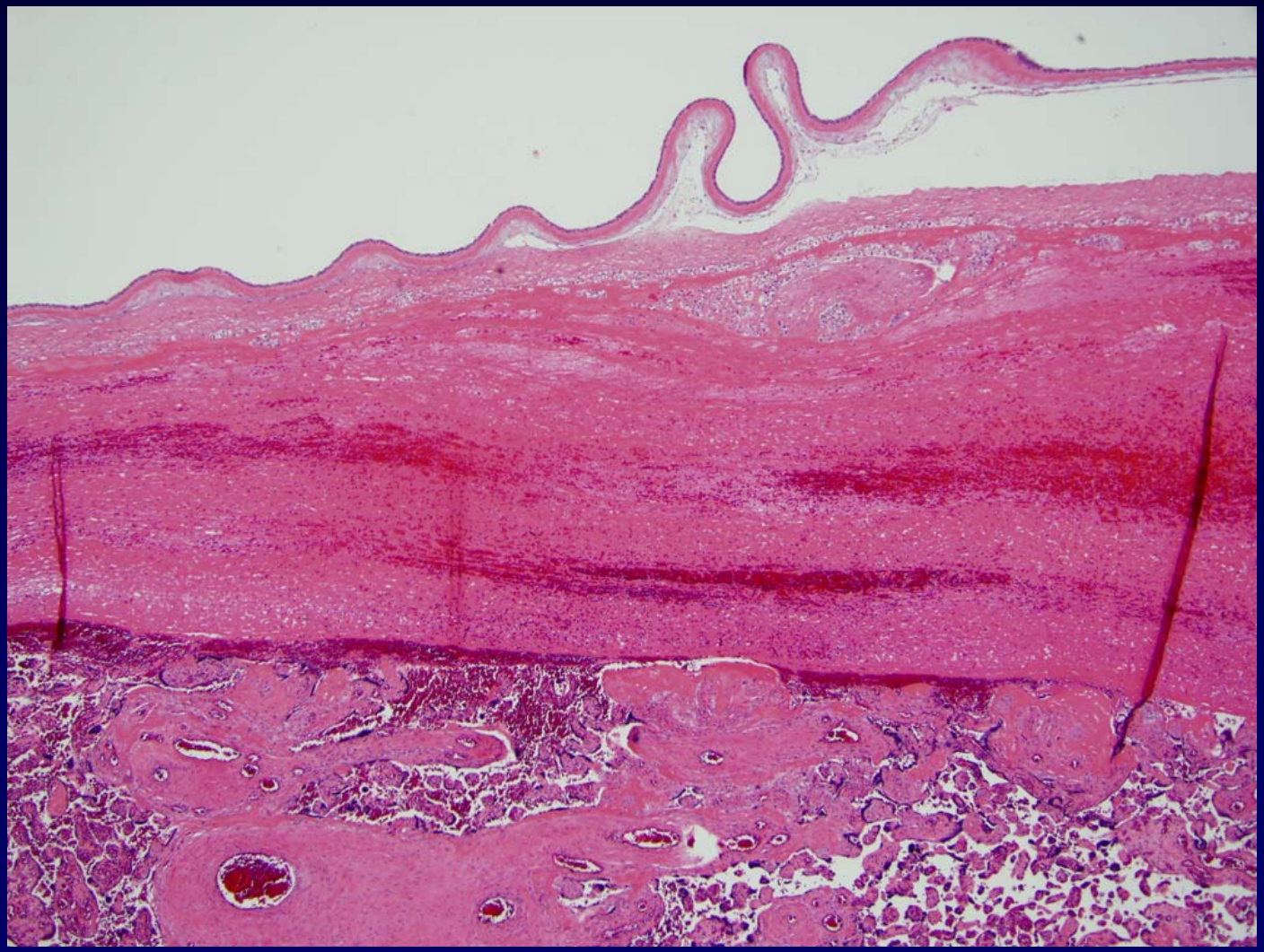
- Stillbirth – 13% to 50%
- Growth retardation - 24 to 100%
- Preterm delivery – 26% to 60%
- Independent predictor of neurologic impairment in preterm infants
- Recurrence – 12% to 78%

Subchorionic Fibrin Deposition

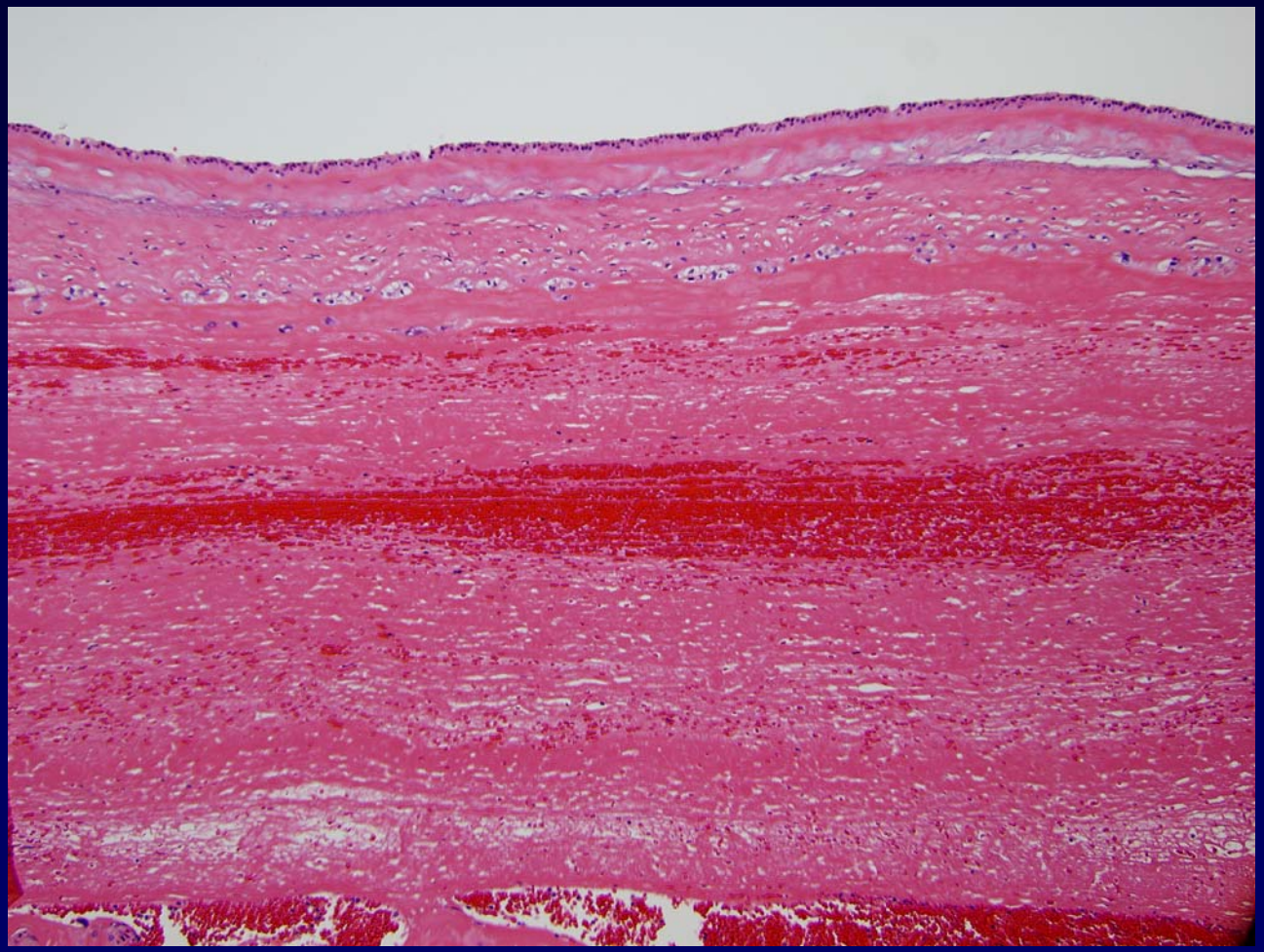


Not clinically significant

Subchorionic Fibrin



Subchorionic Fibrin

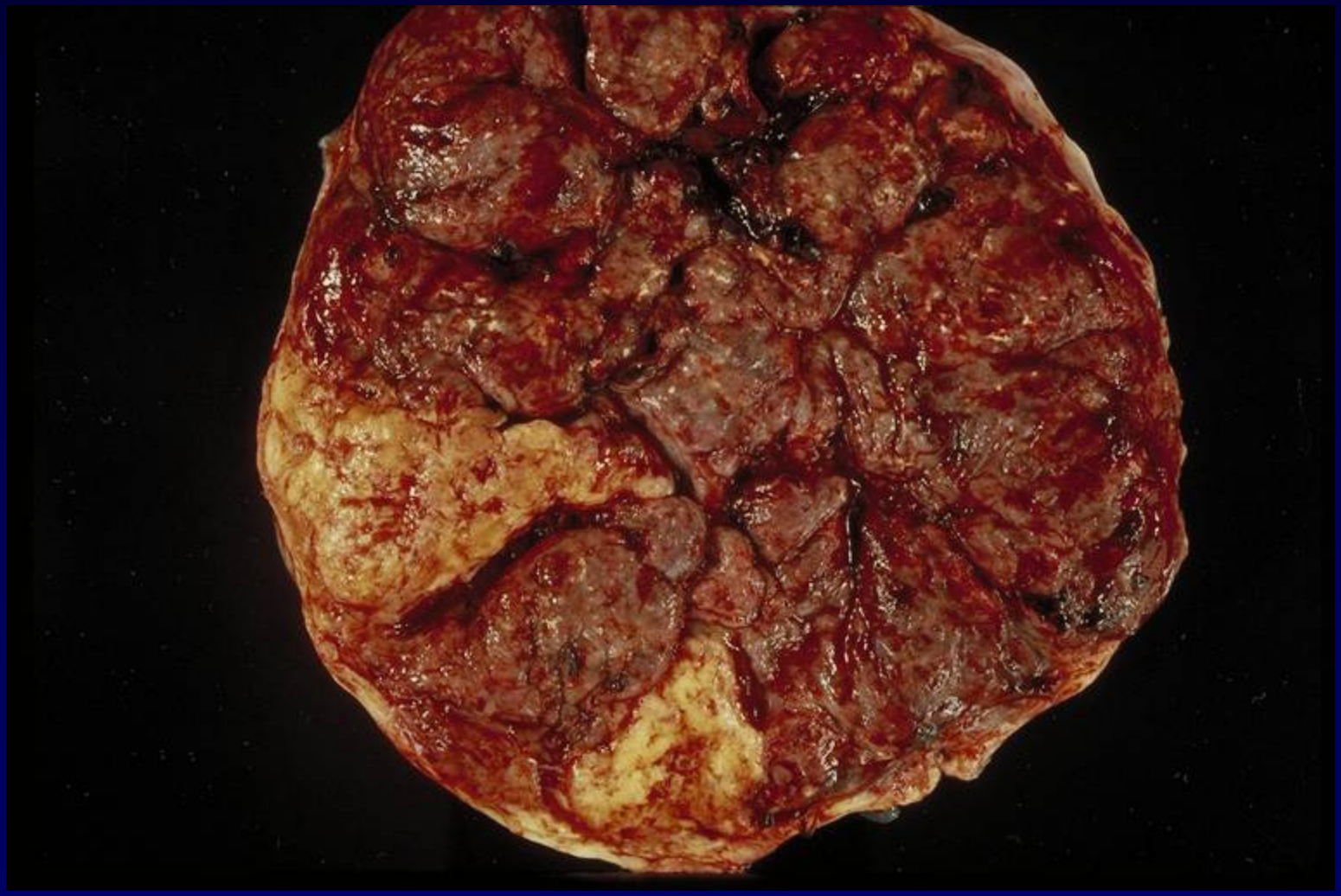


Layers of blood and fibrin beneath chorionic plate

Subchorionic Fibrin

- Not clinically significant
- May reflect damage to fetal plate by fetal movements
- Less common in infants with disorders that restrict movement

Infarcts



Firm, well circumscribed, often pale

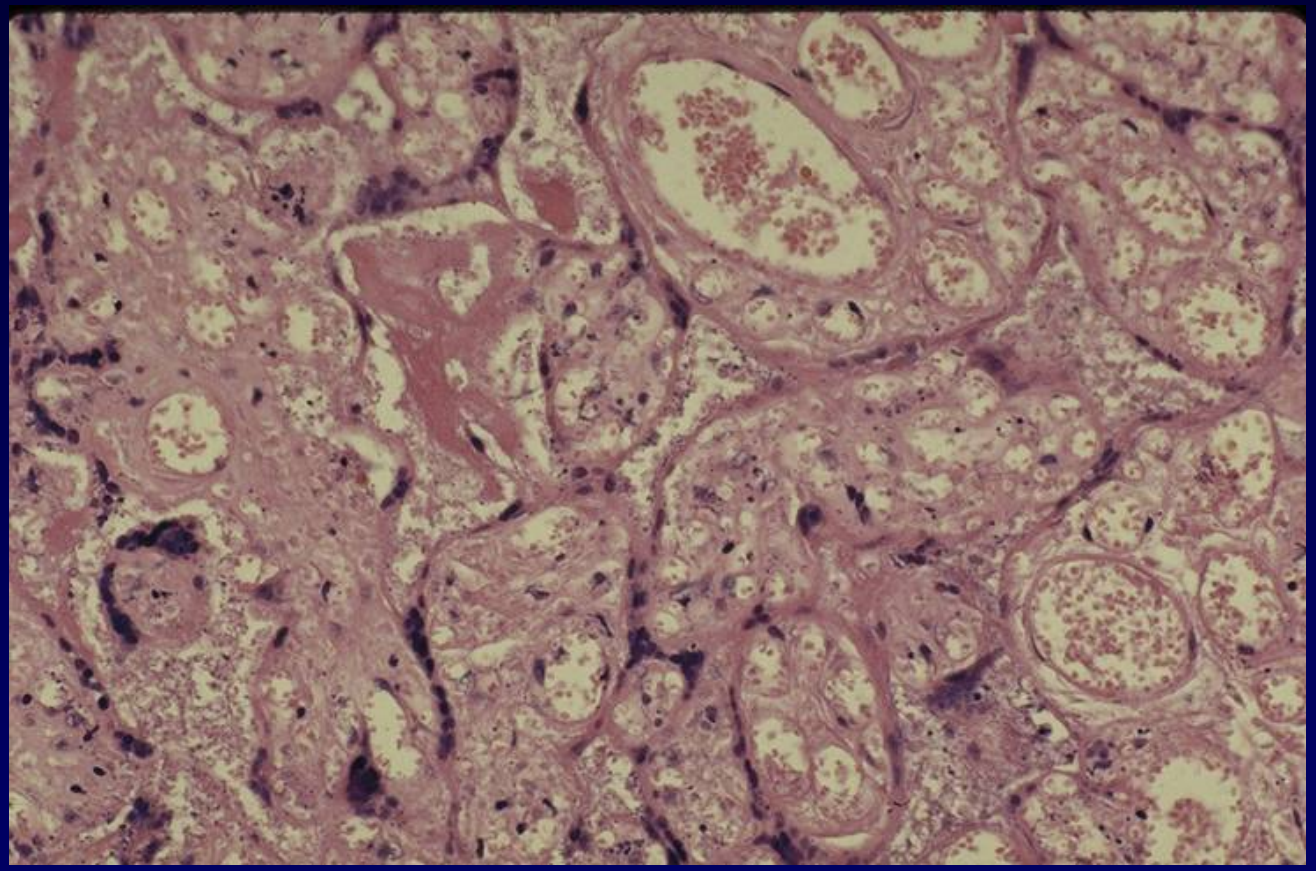
Infarcts

Well circumscribed

Usually abut the maternal surface

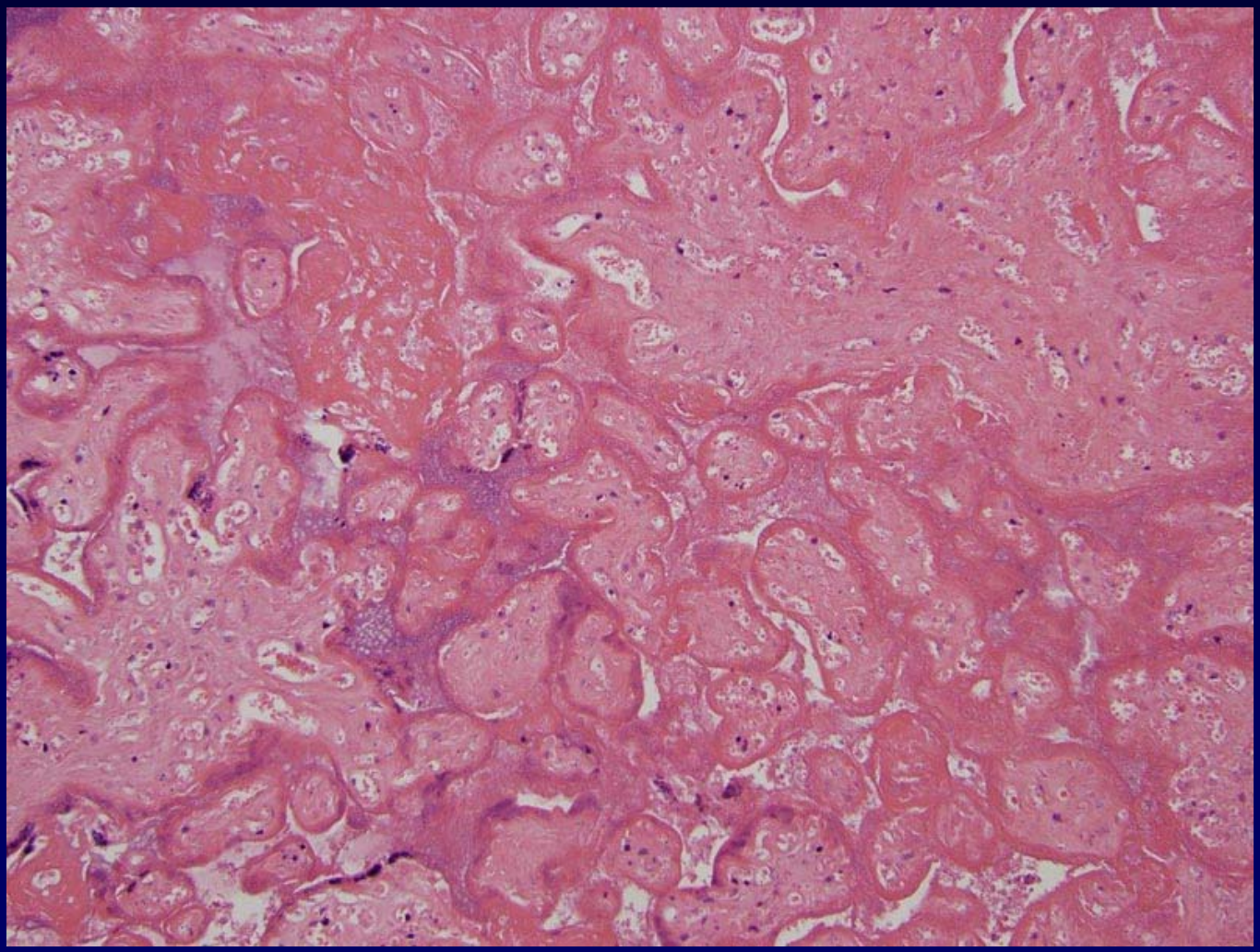
May be red, tan, or white

Infarcts



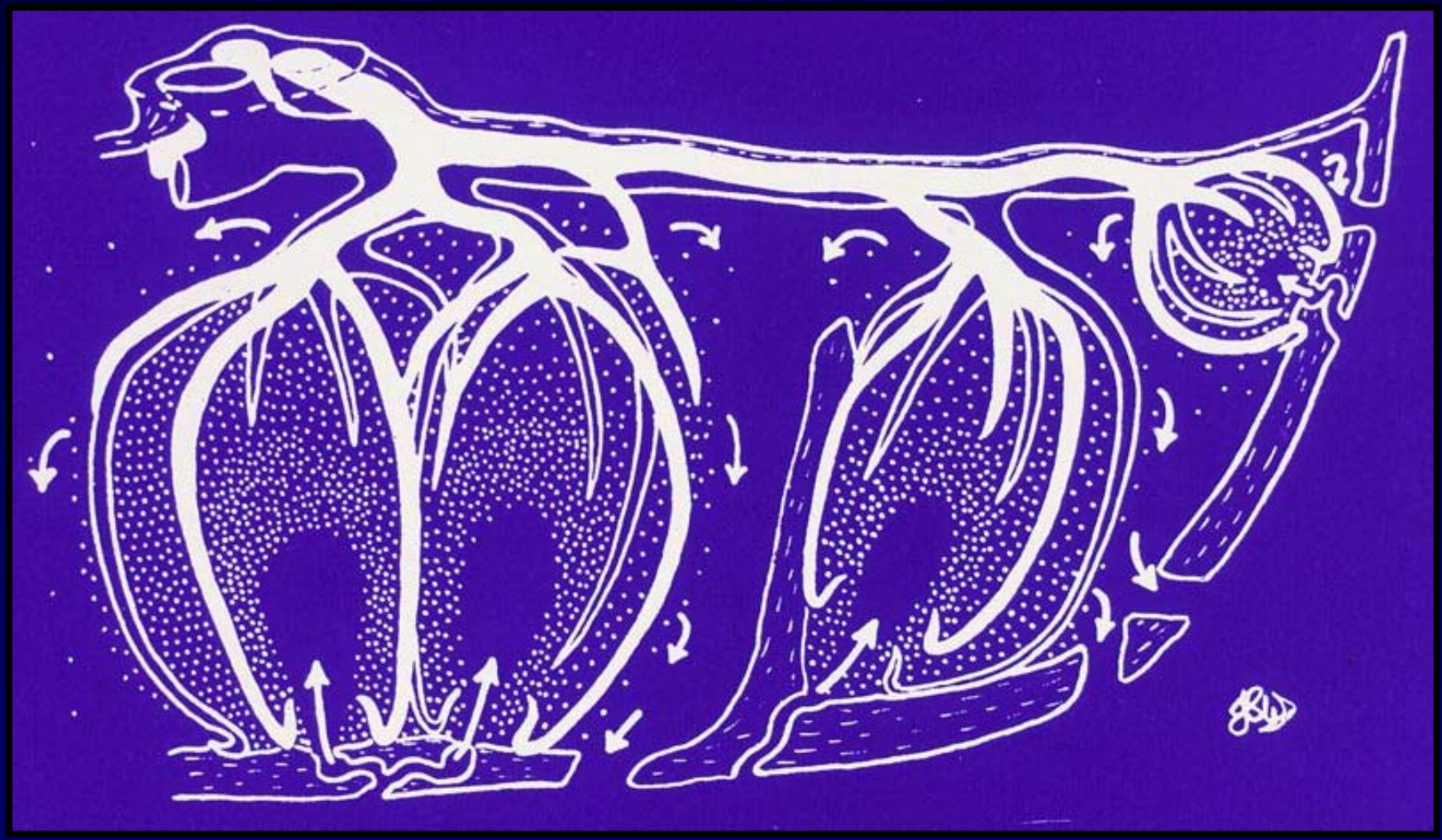
Loss of intervillous space

Infarcts



Ghost villi with thick trophoblast membranes

Placental Perfusion



Infarcts

Pathogenesis

- Decreased blood supply to group of villi
  - Vessel narrowing (hypertension)
  - Atherosis (preeclampsia)
  - Physical separation (retroplacental hematoma)

Infarcts

Normal

- See in 10-25% of term placentas
- Small, located in periphery

Clinically significant if:

- Multiple, central
- Large (>3 cm)
- Preterm

Infarcts

Clinical significance for fetus

- Hypoxia
- Intrauterine growth restriction
- Periventricular leukomalacia (preterm)
- Intrauterine fetal demise

Infarcts

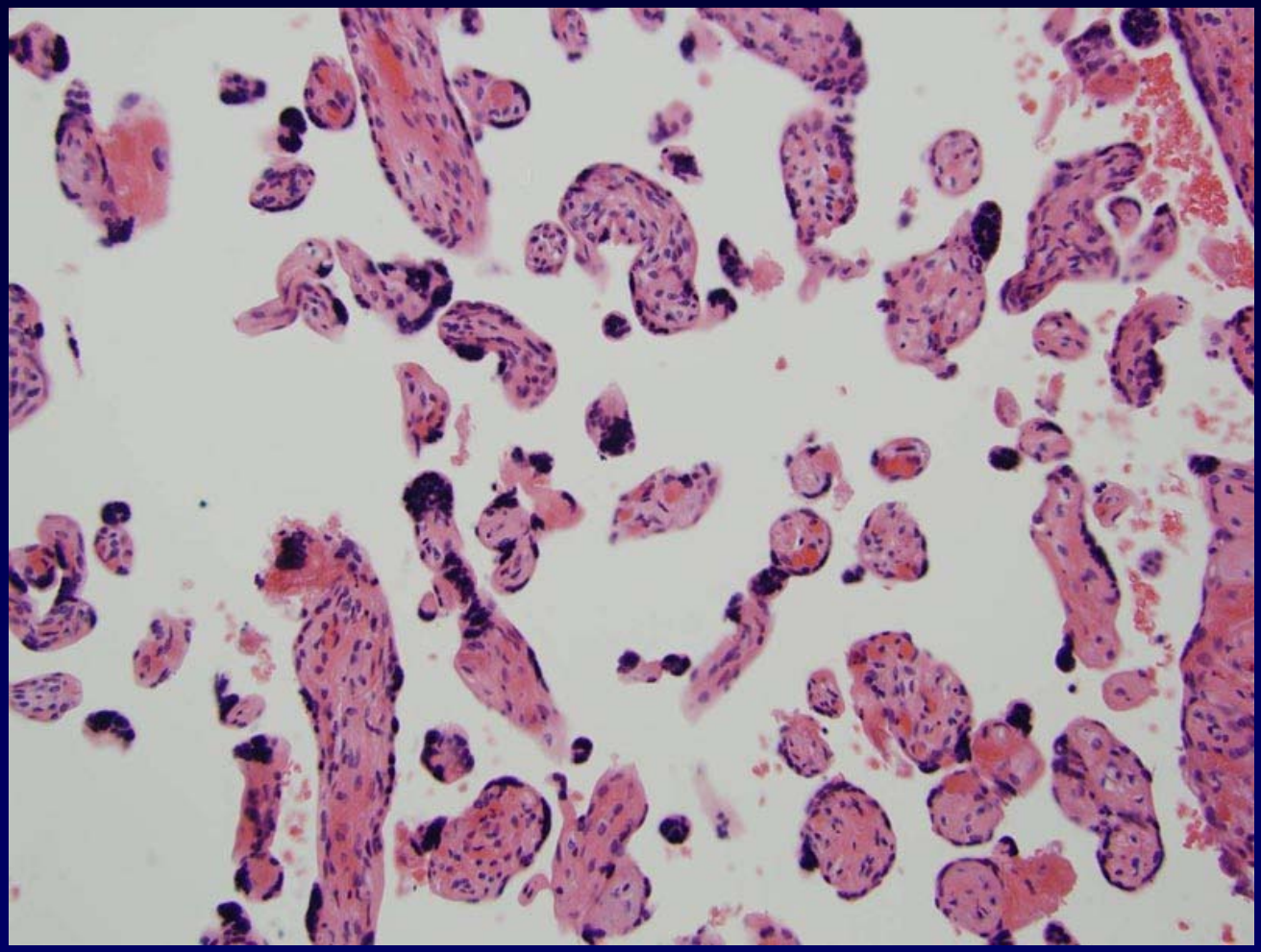
Clinical significance for the mother

- Extensive implies significant maternal disease
- Preeclampsia - severity related to extent of infarction
- Maternal thrombophilic conditions

Infarcts

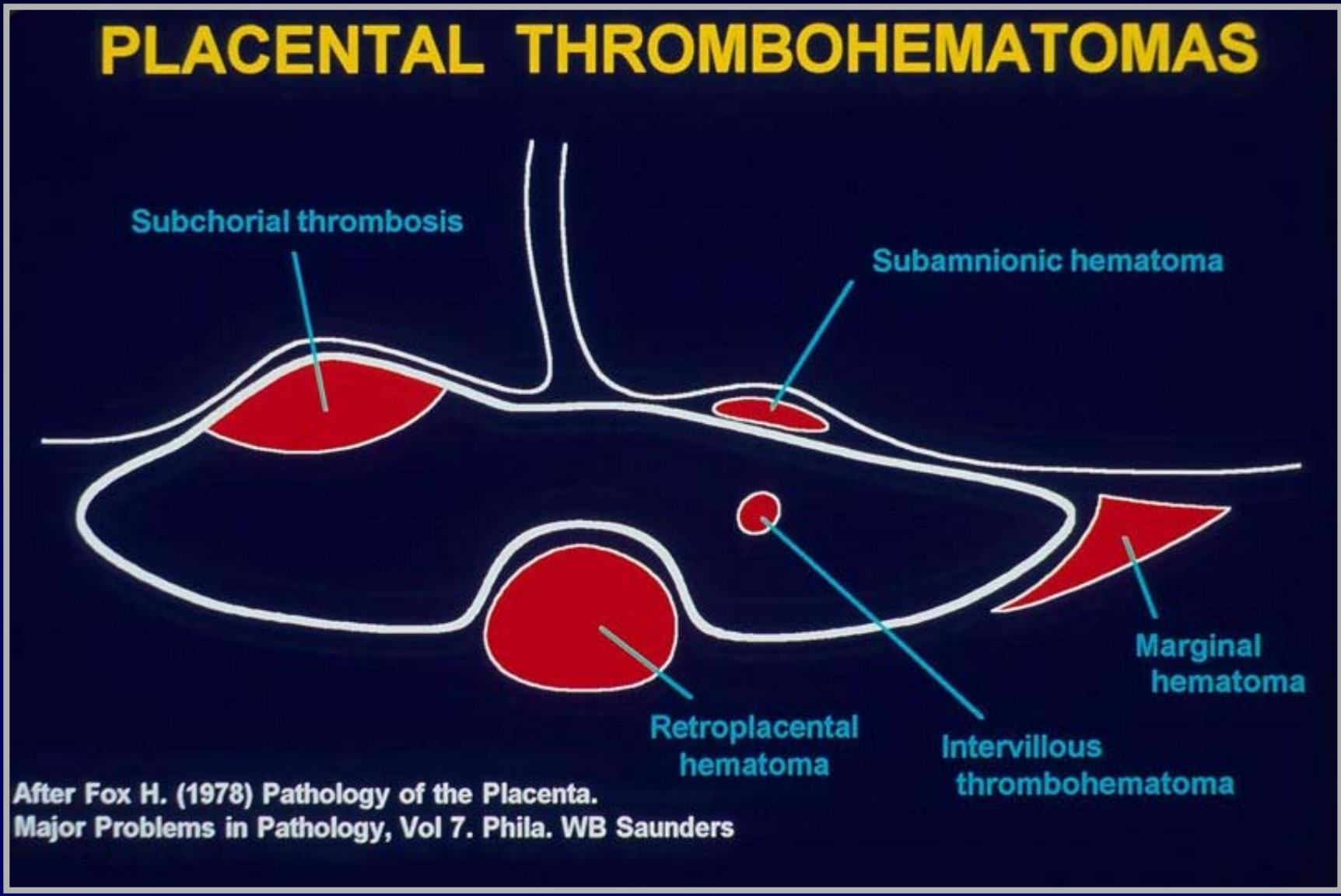
- Sample areas away from infarcts
  - Determine overall perfusion of placenta
  - Small, narrow villi, few vessels, increased knots indicates poor perfusion
- Normally perfused placenta can lose 20% of villi without harming infant
- Less reserve if already poorly perfused

Low Flow Changes



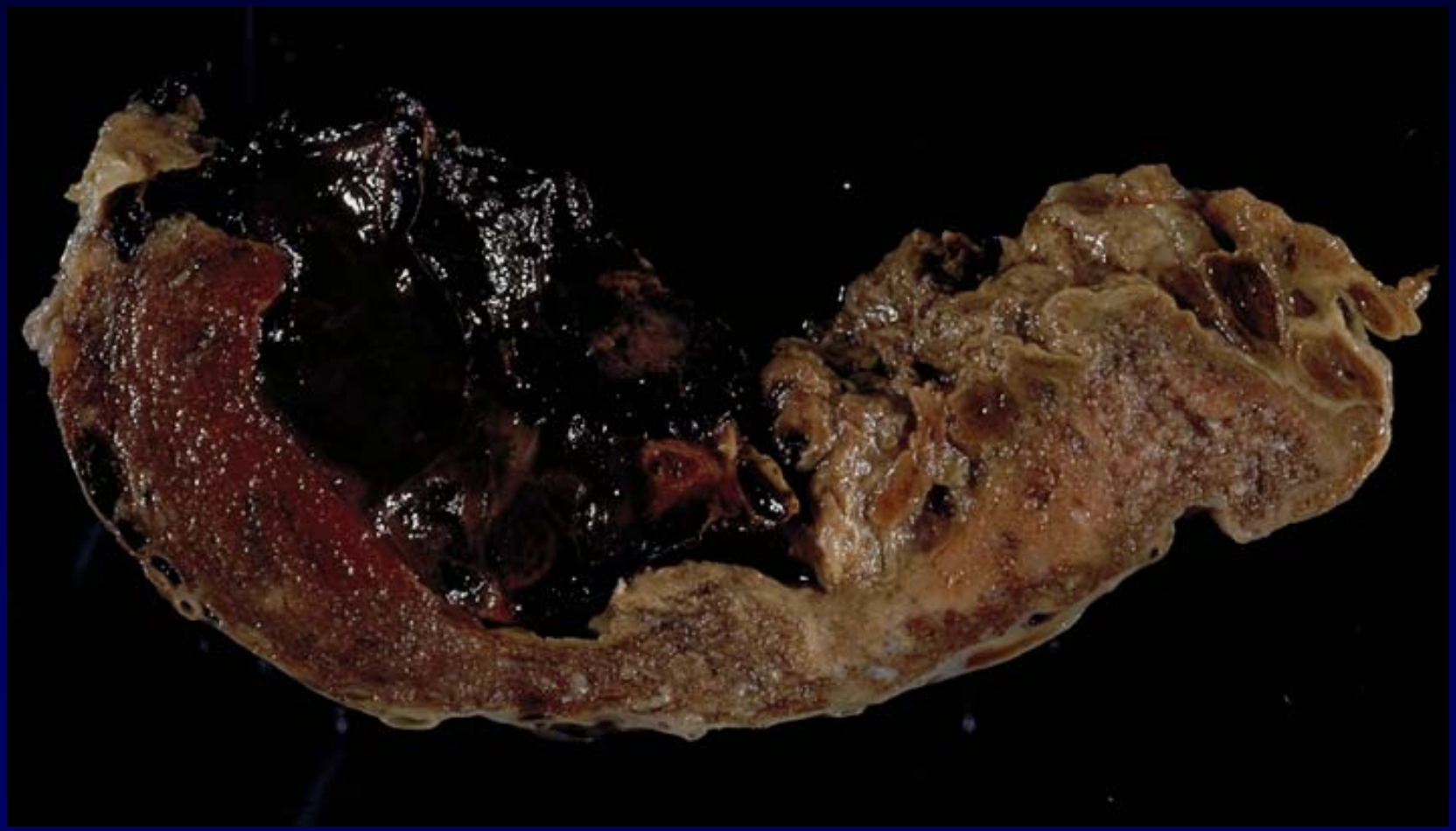
Small, thin, unbranched villi
Increased syncytial knots

PLACENTAL THROMBOHEMATOMAS



After Fox H. (1978) Pathology of the Placenta.
Major Problems in Pathology, Vol 7. Phila. WB Saunders

Retroplacental Hematoma

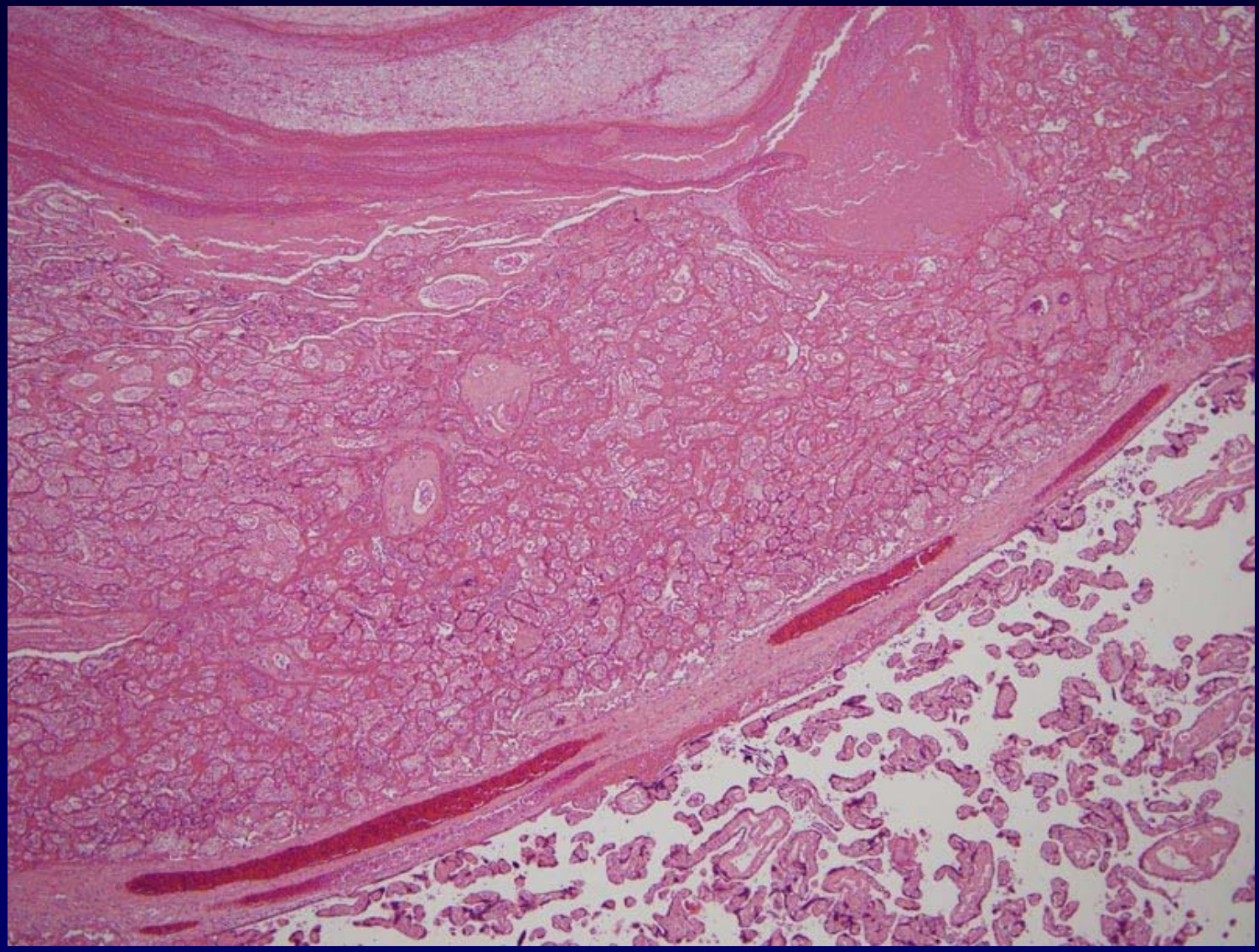


Blood clot indents placenta, underlying infarction

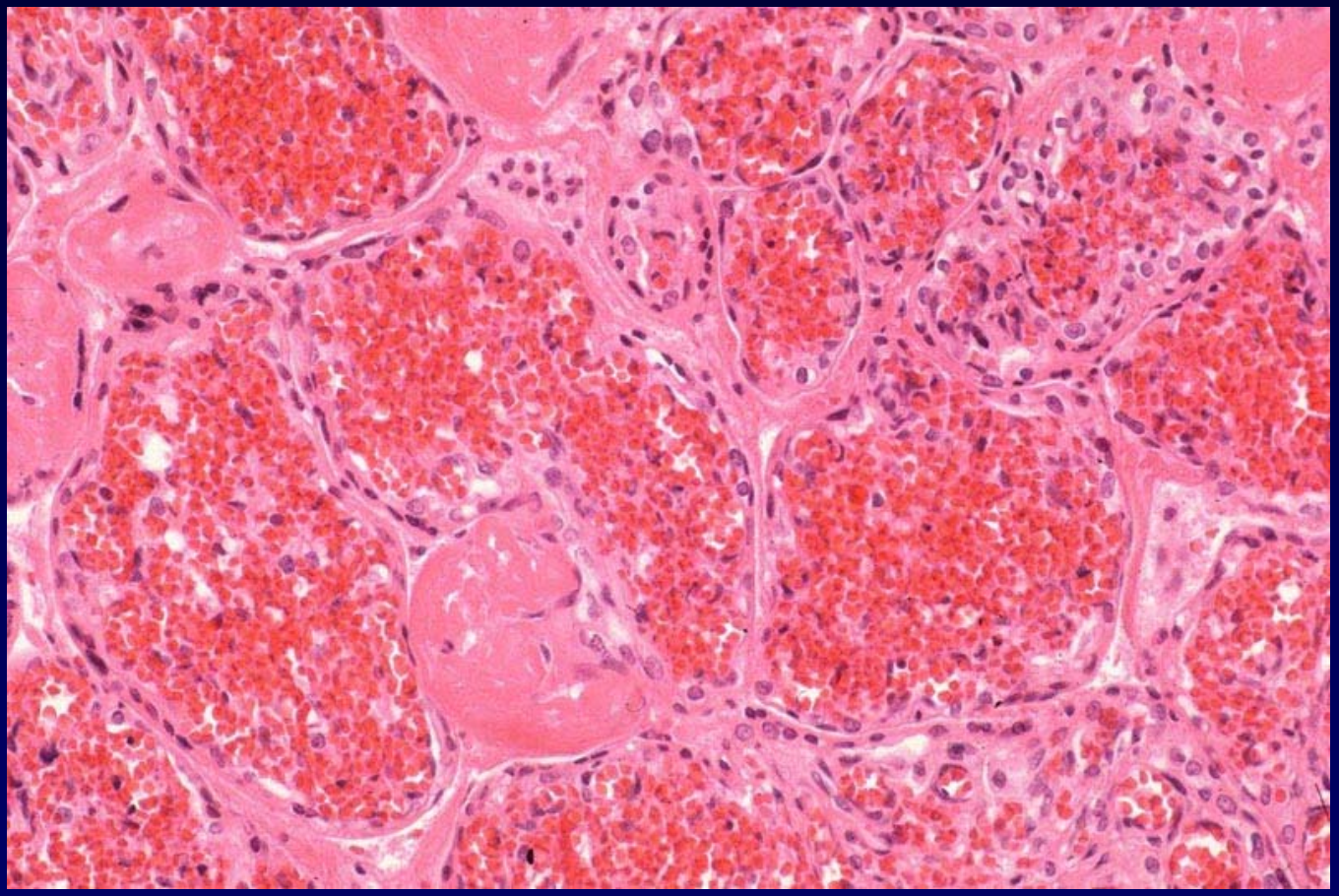
Retroplacental Hematoma

Densely adherent clot indents surface, underlying infarction

Retroplacental Hematoma



Retroplacental Hematoma



Villous stromal hemorrhage may be seen beneath, especially in the 2nd trimester

Retroplacental Hematoma

Incidence ~ 5%

Clinical associations

- Preeclampsia
- Heavy smoking, cocaine
- Trauma
- Acute chorioamnionitis
- Maternal thrombophilic conditions
- Prior abruption

Retroplacental Hematoma

Postulated pathogenesis

- Atherosis (preeclampsia) – weakened vessels
- Cocaine, cigarettes – spasm
- Thrombophilia - thrombosis

Placental Abruption

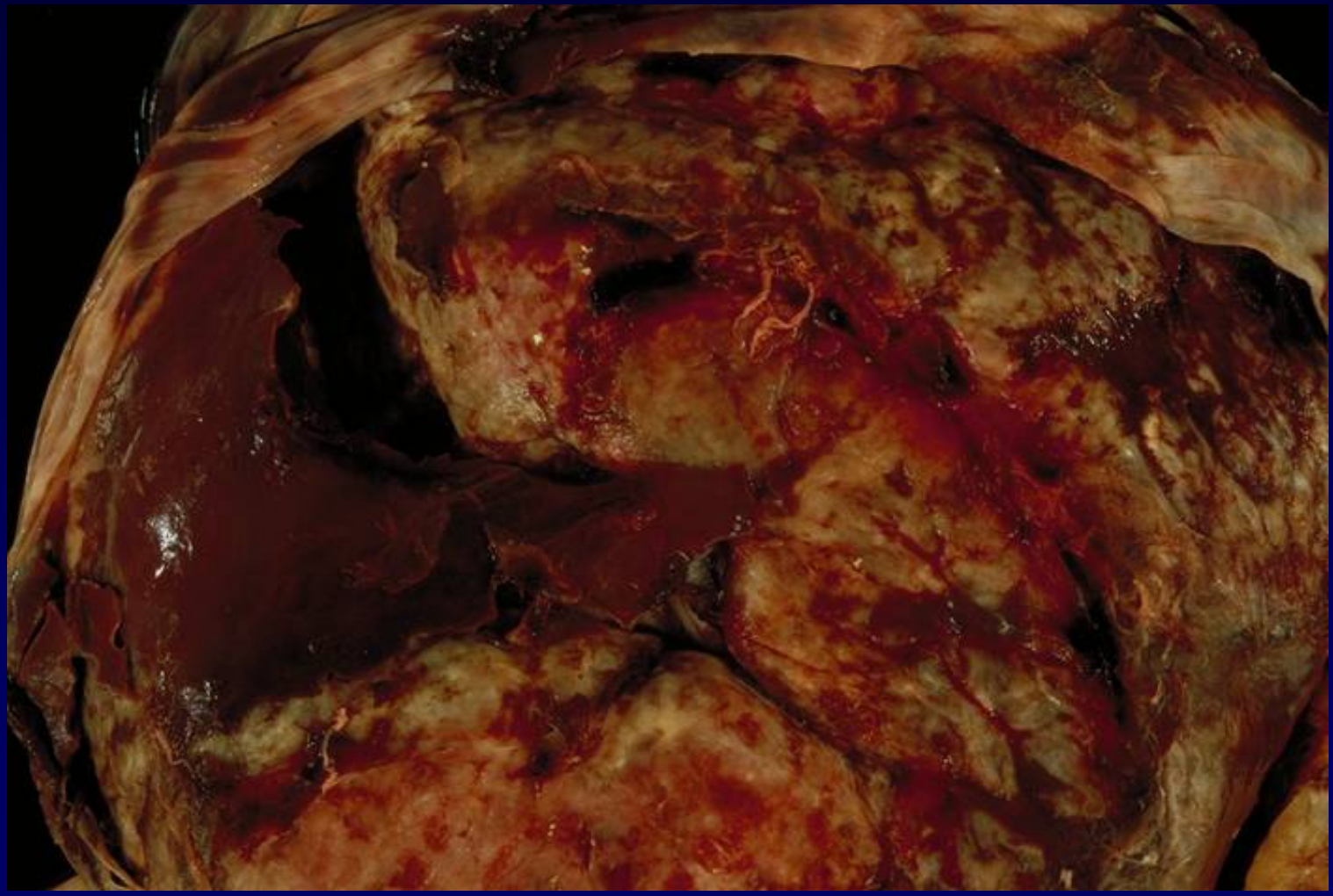
A clinical syndrome

- Vaginal bleeding
- Increased uterine tone
- Uterine tenderness
- Decreased fetal heart tones
- Maternal hypotension, DIC

Retroplacental Hematoma

- 30% with abruption have hematoma
- 35% with hematoma have abruption
- Clinical significance
  - Depends on size, amount of infarction, how well rest of placenta is perfused
  - Fetal death
  - Periventricular leukomalacia (preterm)

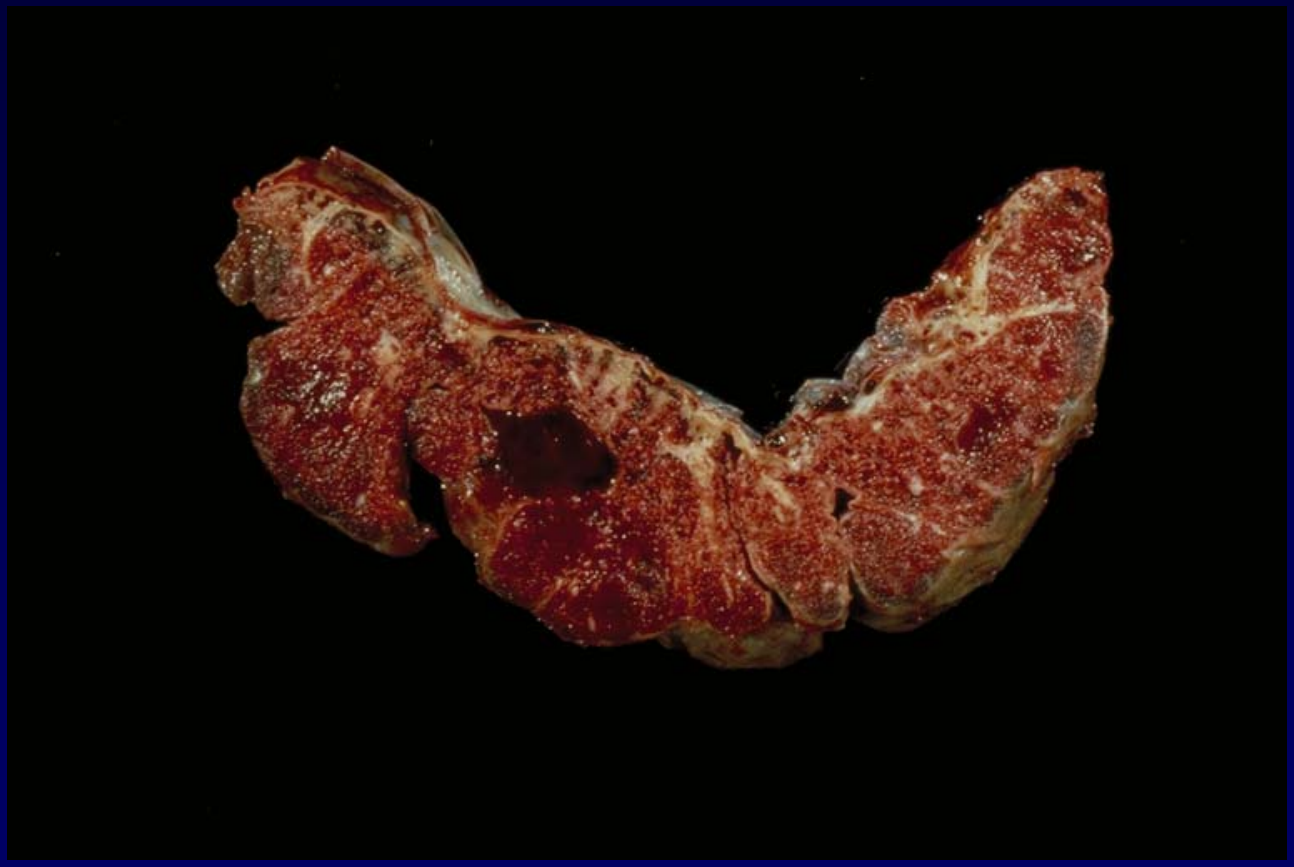
Marginal Hematoma



Marginal Hematoma

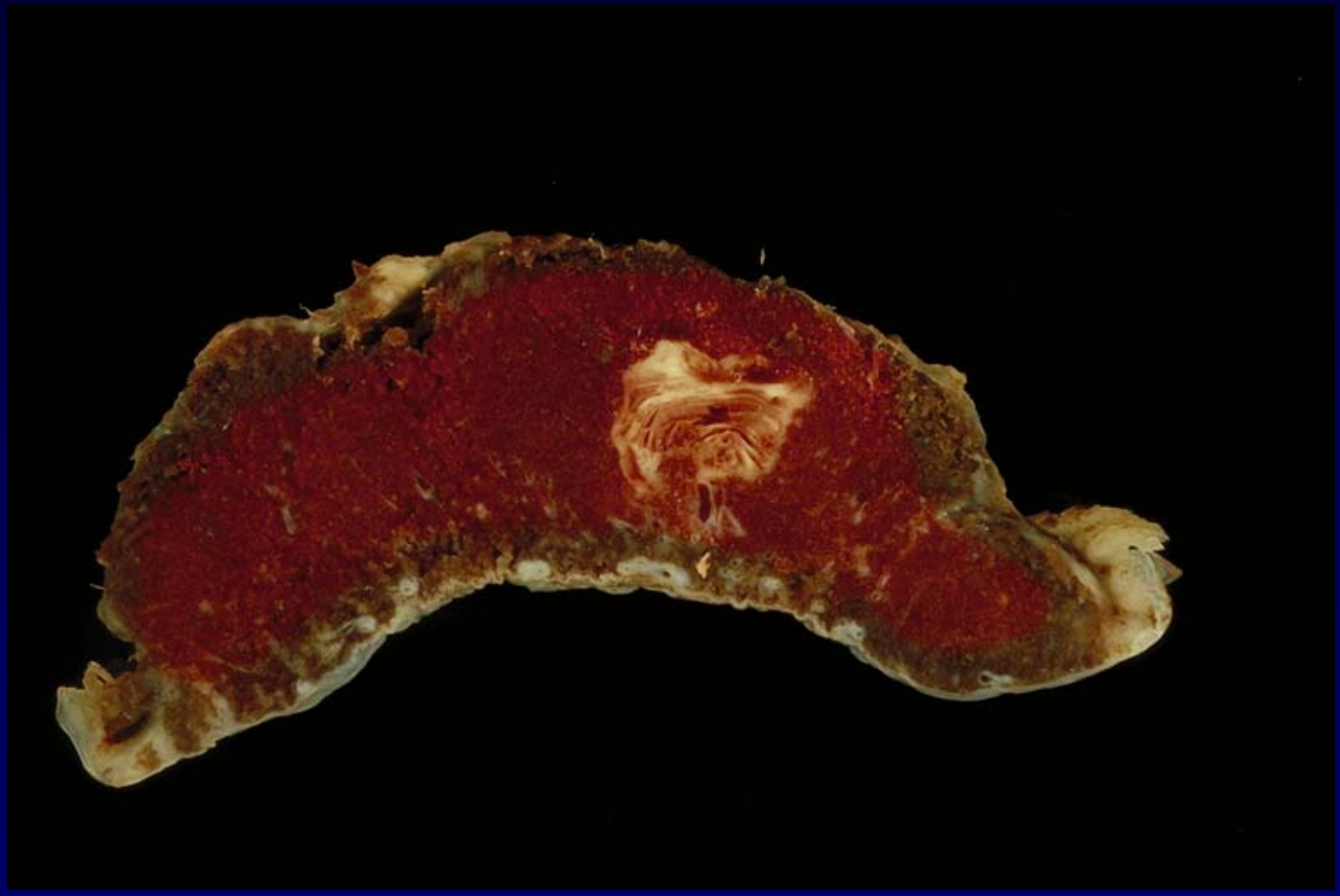
- Blood clot located between disc edge and membranes
- Often associated with hematoma on membranes
- Occurs in placentas implanted close to os
- Causes bleeding during delivery
- Clinically mistaken for “abruption”
- Not clinically significant – no associated infarction

Intervillous Thrombohematoma



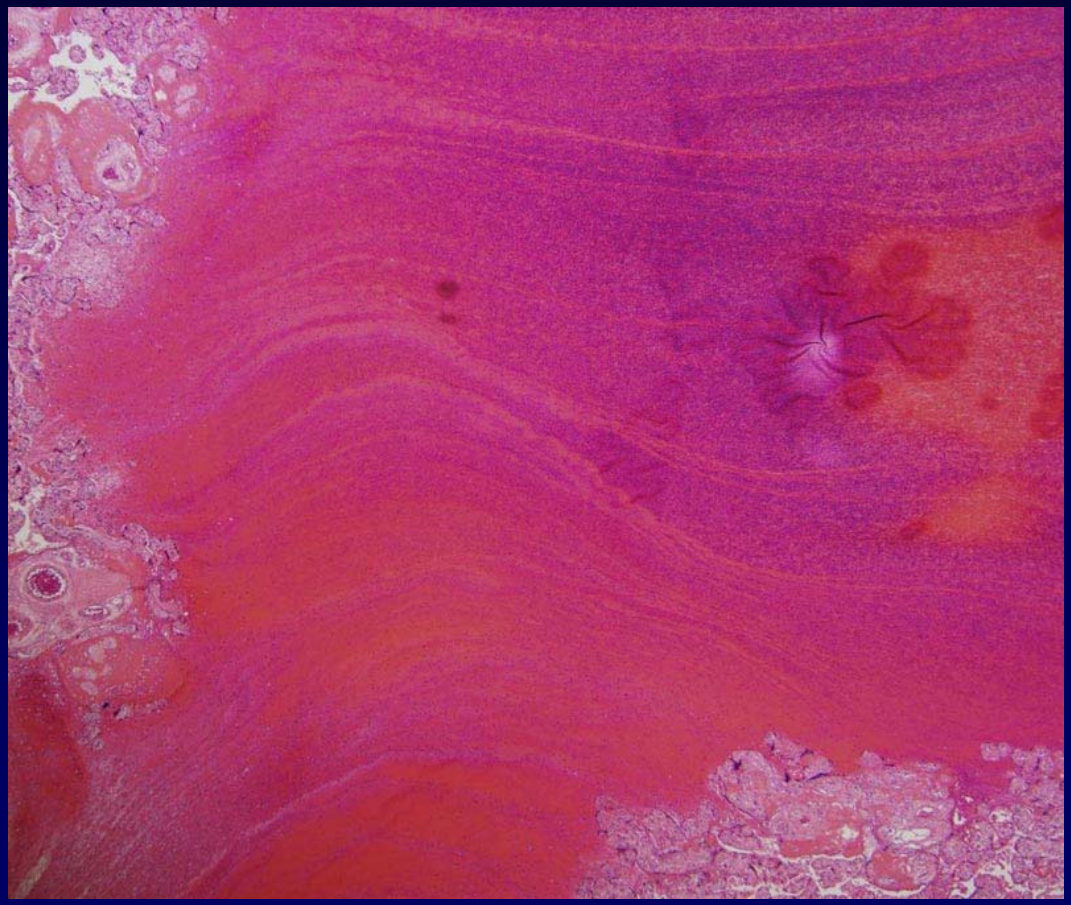
Midway between fetal and maternal surfaces

Intervillous Thrombohematoma



Well circumscribed, laminated, red if early, white if older

Intervillous Thrombohematoma



Laminated
Pushes villi to the side

Intervillous Thrombohematoma

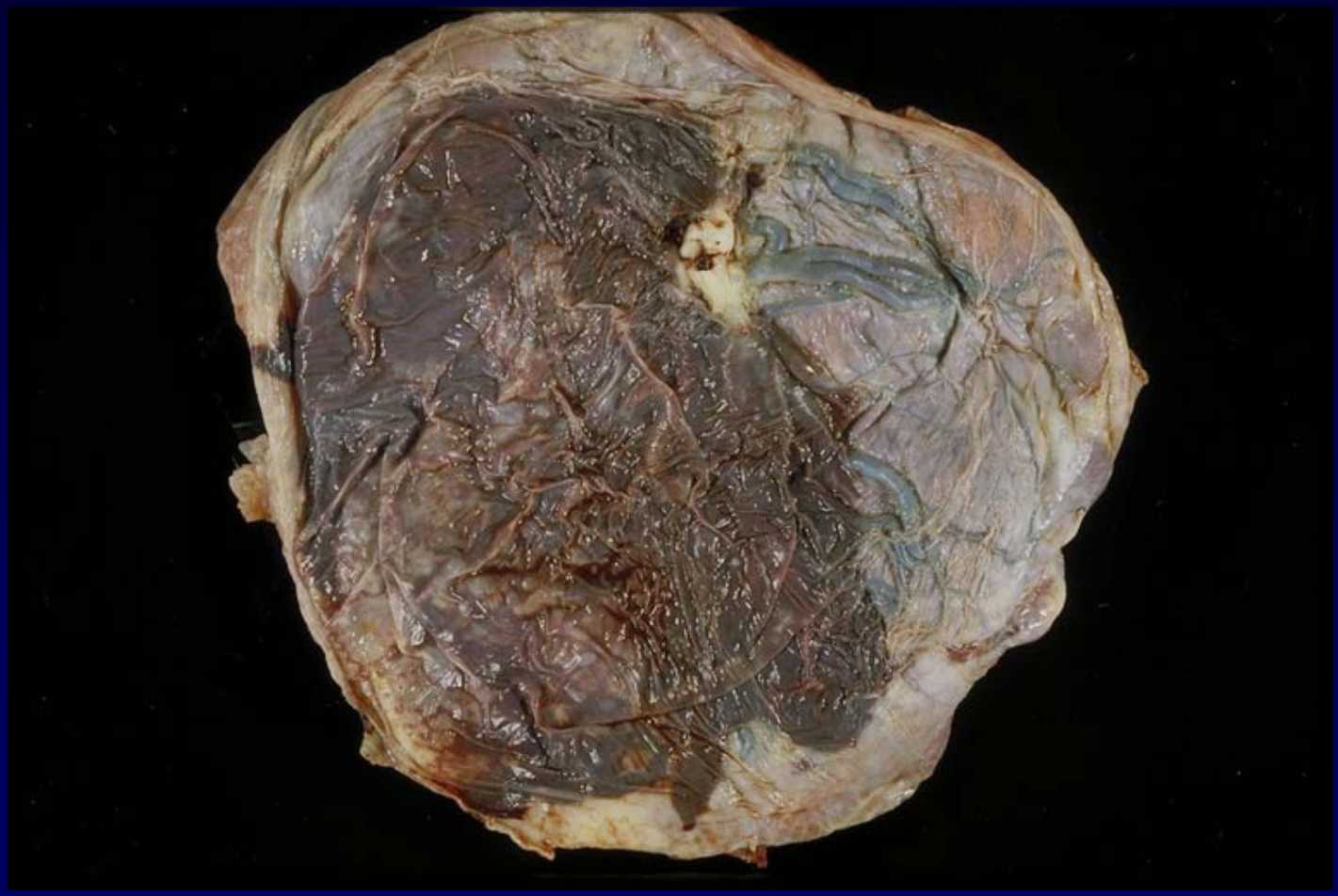
- Common
  - 50% of normal placentas
  - 78% of placentas from complicated pregnancies
- Small
  - Mean size 1.5 cm
  - Often multiple

Intervillous Thrombohematoma

Clinical significance

- Marker of maternal fetal hemorrhage
  - Lesions have maternal and fetal blood
- Fetal anemia, thrombocytopenia
- Fetal death - if large
- Maternal sensitization

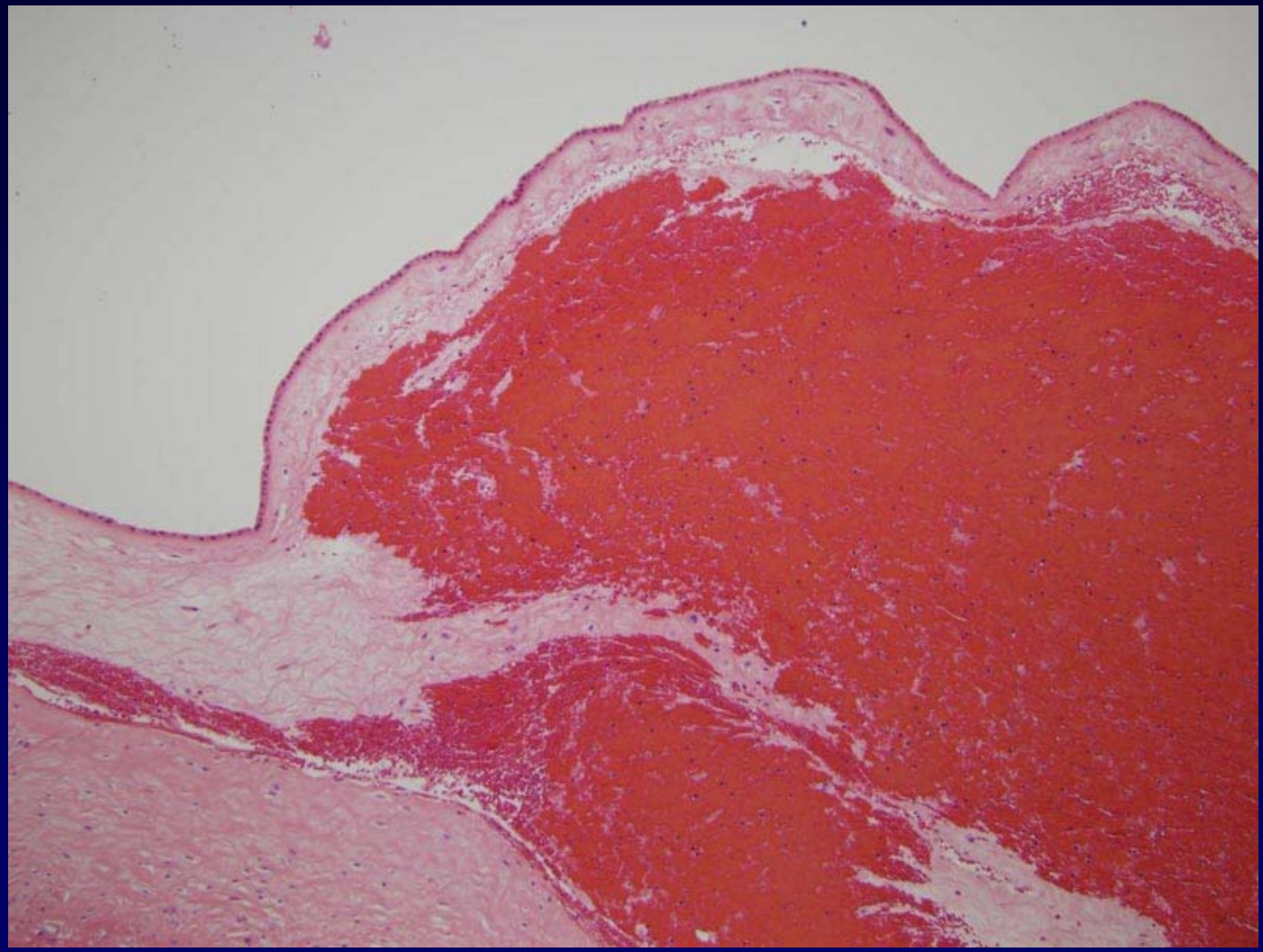
Subamniotic Hematoma



Liquid blood

Laceration of surface vessels with cord traction

Subamnionic Hematoma



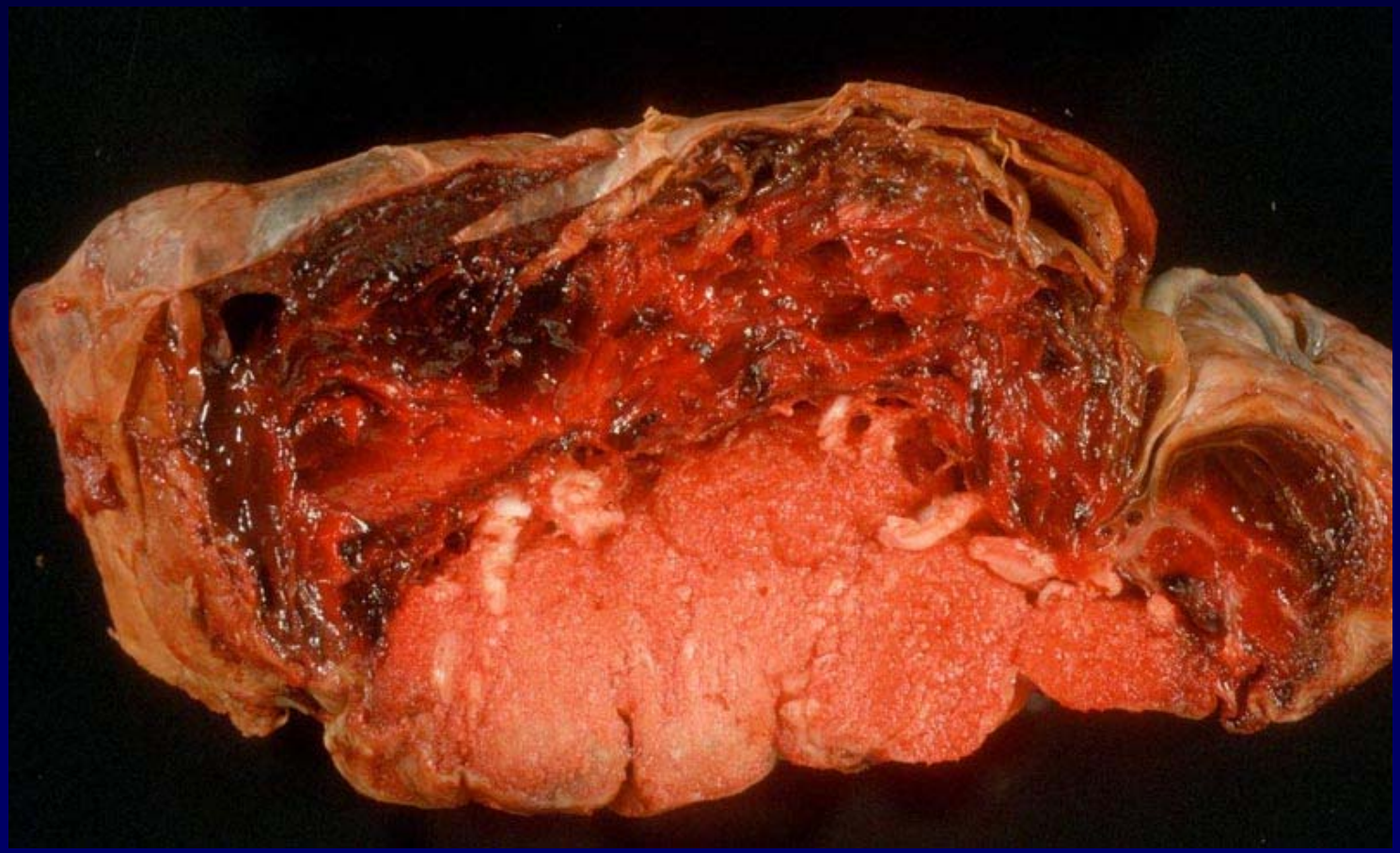
Blood dissects between amnion and chorion

Subamniotic Hematoma

Bleeding due to laceration of surface vessels

- Traction on cord
  - After delivery of baby
  - Not clinically significant
- Iatrogenic laceration of surface vessels
  - Amniotic fluid sampling for lung maturity
  - Intrauterine transfusion
  - Could be clinically significant

Massive Subchorial Thrombosis
Breus' Mole



Red clot, 1 cm thick beneath chorion

Massive Subchorial Thrombosis
Breus' Mole

- Rare - 0.53/1000 examined placentas
- Intrauterine growth restriction - 40%
- High rate of stillbirth and neonatal death

Massive Subchorial Thrombosis Breus' Mole

Pathogenesis

- Sudden marked stasis in intervillous space
- Rupture of large chorionic plate or stem villous vessel
- Clot may impede blood flow through cord vessels

Circulatory Disorders

Disorders of the maternal circulation

- Massive perivillous fibrin deposition
- Maternal floor infarct
- Subchorionic fibrin deposition
- Infarcts
- Retroplacental hematoma
- Marginal hematoma
- Intervillous thrombohematoma
- Subamniontic hematoma
- Massive subchorial thrombosis (Breus' mole)

Circulatory Disorders

Disorders of the fetal circulation

- Fetal vascular obstruction
- Chorangioma
- Chorangiosis

Fetal Vascular Obstruction

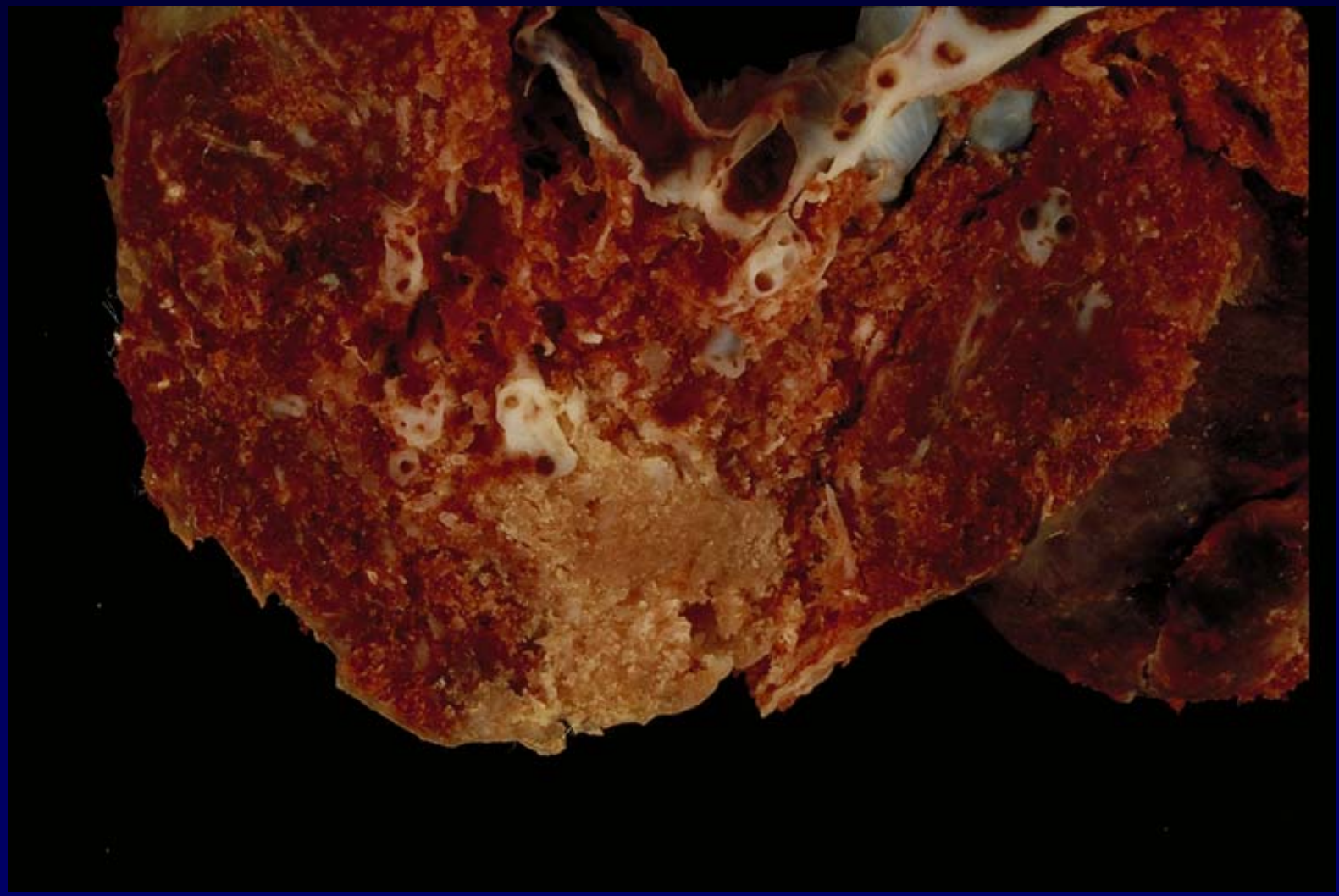
May occur at any level

- Umbilical cord vessels
- Chorionic plate vessels
- Small vessels in villi

Fetal Vascular Obstruction

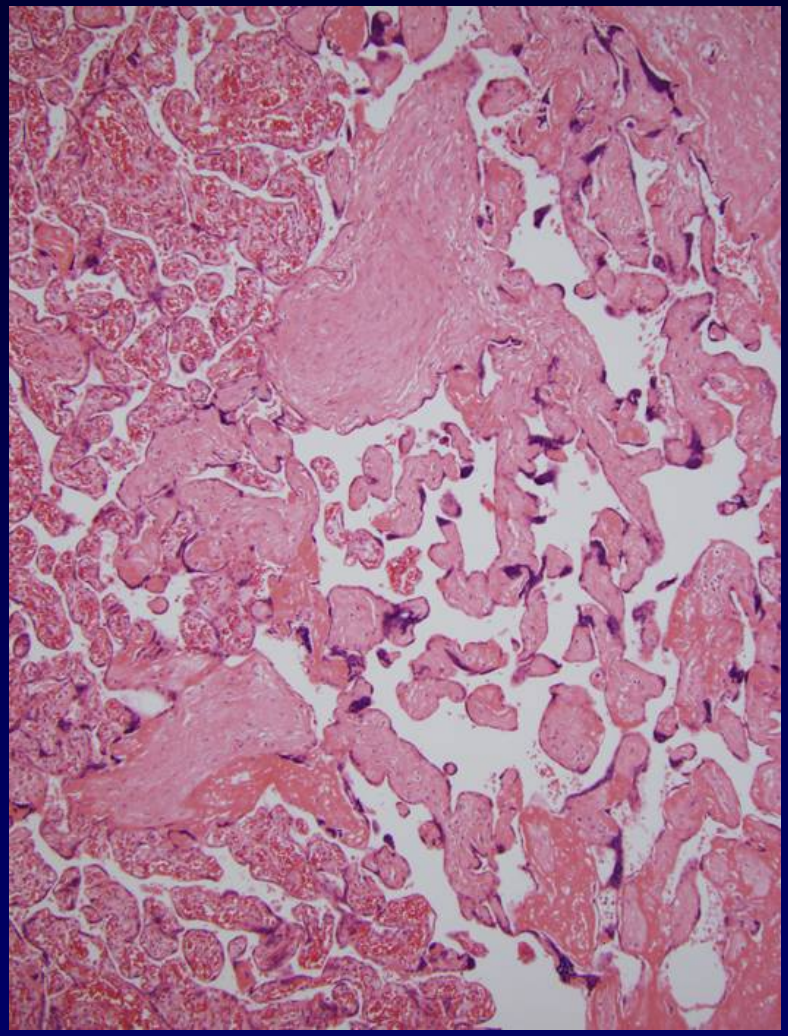
- Fetal circulation of placenta and of fetus itself are connected
- Vascular obstruction in fetal circulation of placenta may be associated with thrombotic or embolic lesions in circulation of fetus

Fetal Vascular Obstruction



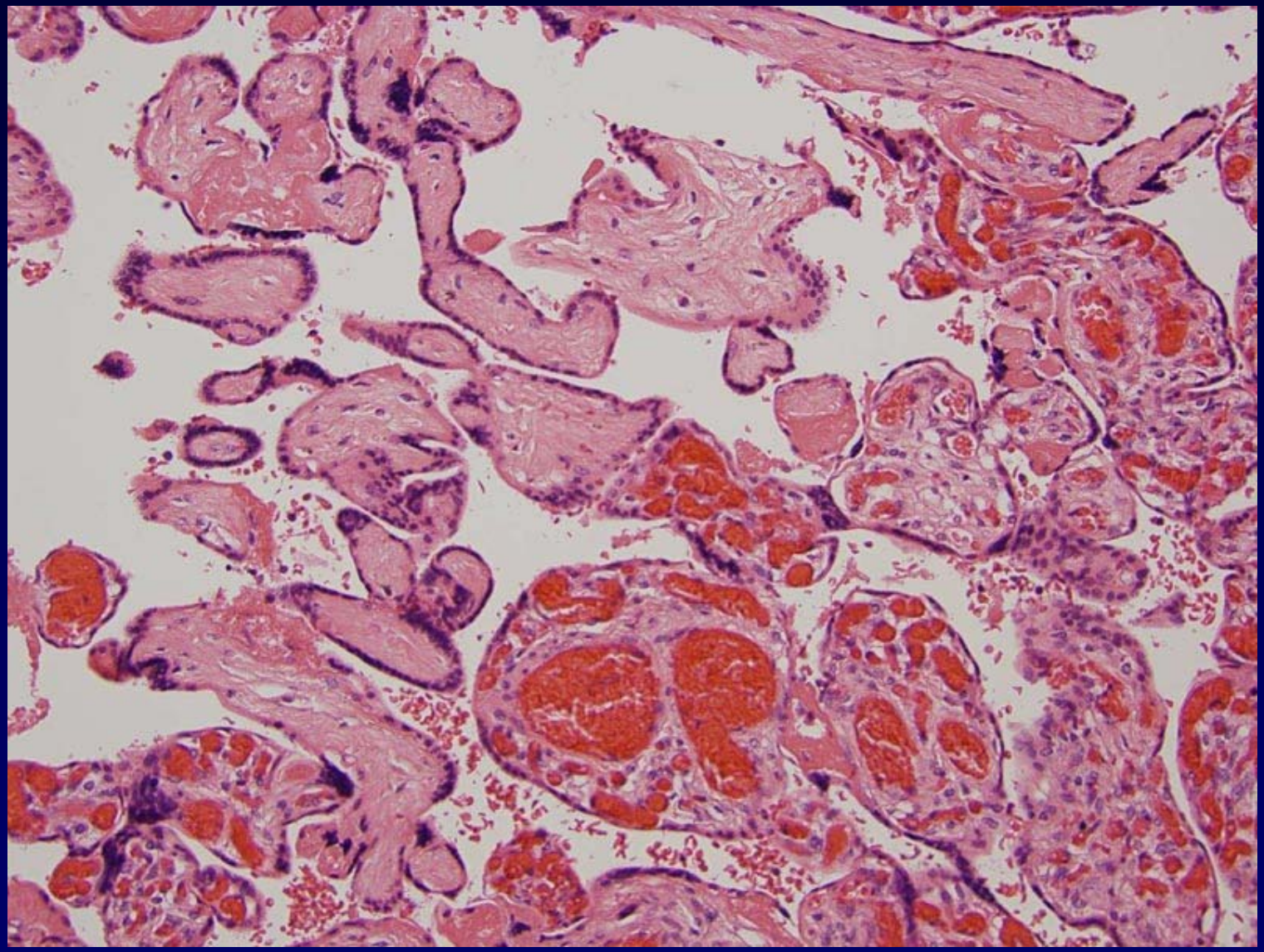
Well circumscribed, pale but *not* firm

Fetal Vascular Obstruction

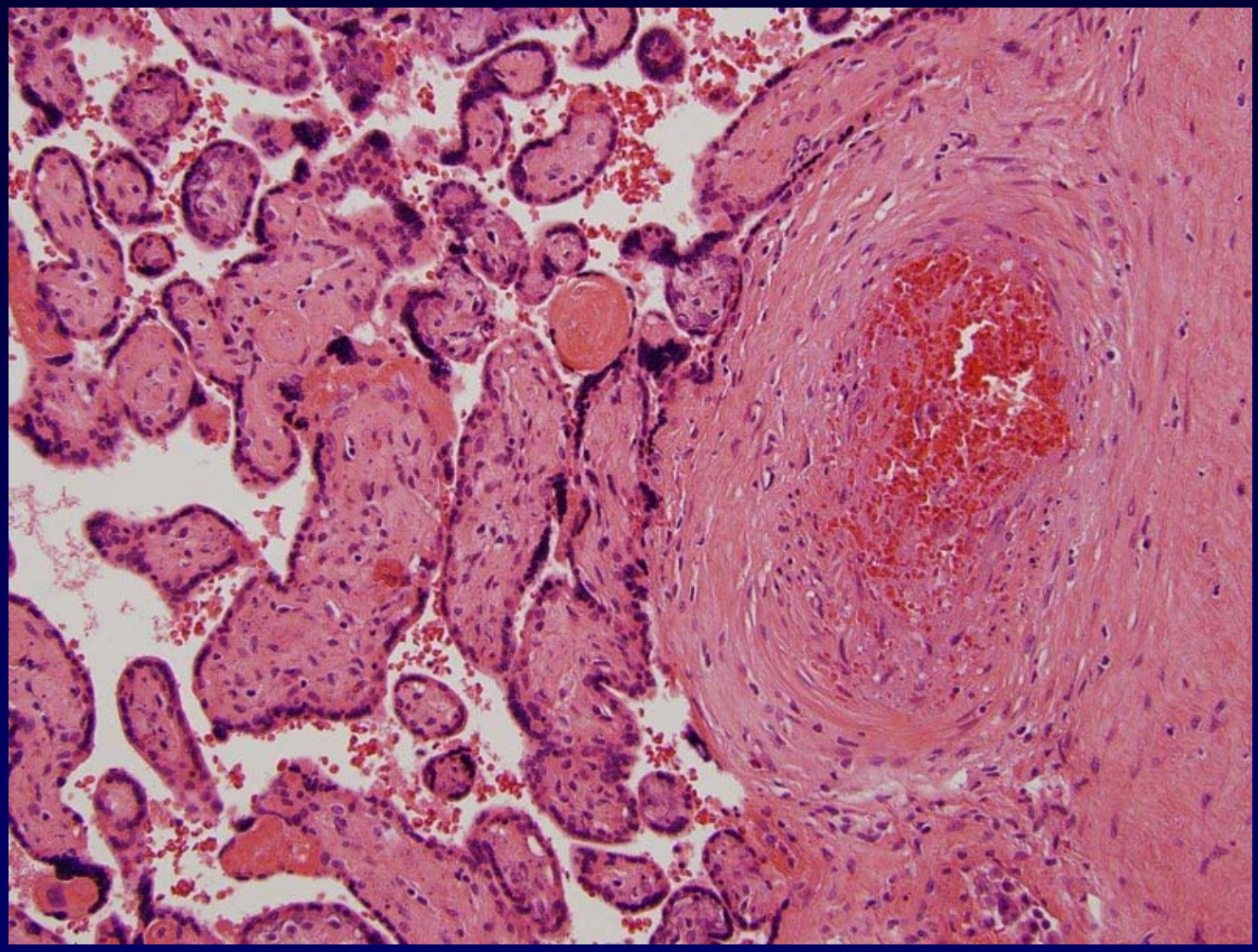


Well circumscribed area of pale, fibrotic villi

Fetal Vascular Obstruction

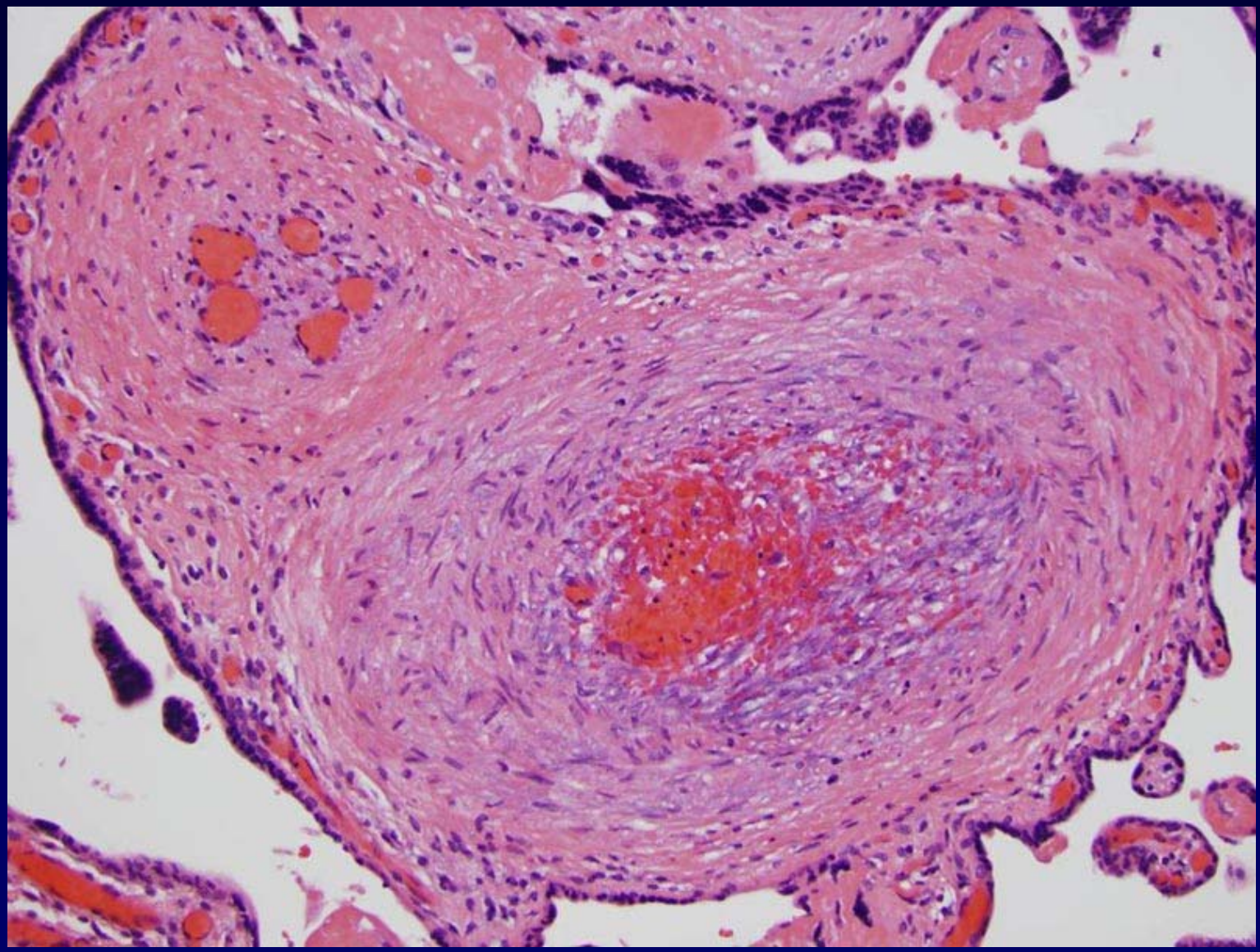


Fetal Vascular Obstruction

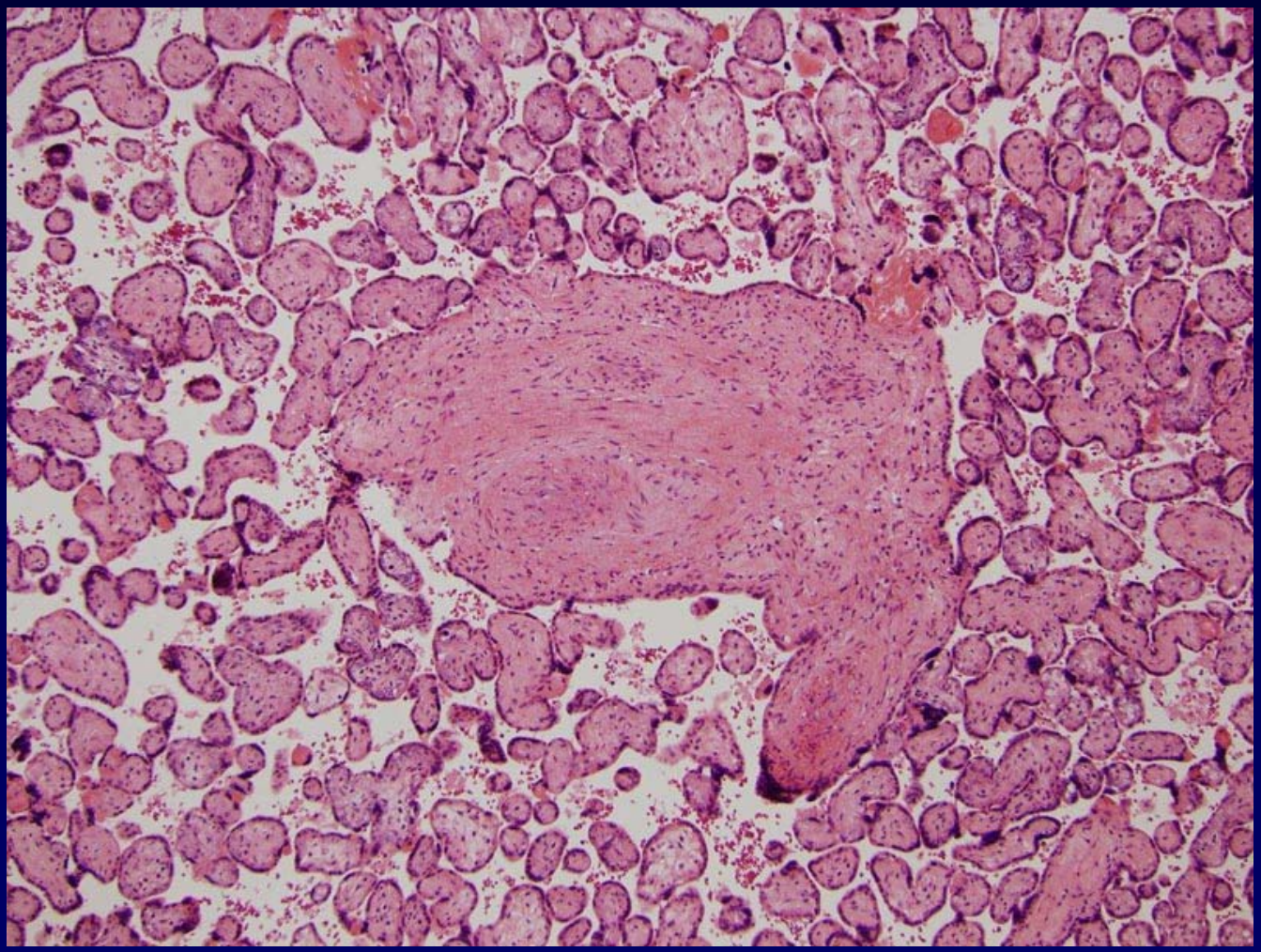


Thrombosis of larger vessels, downstream avascular terminal villi

Fetal Vascular Obstruction



Fetal Vascular Obstruction



Sclerosis of vessels in higher order villi, avascular terminal villi

Fetal Vascular Obstruction

Recently proposed terminology

- Uniformly avascular villi

  Three or more foci of two or more villi are avascular

Redline RW et al. Pediatr Dev Pathol 2004; 7:443-452

Fetal Vascular Obstruction

Recently proposed terminology

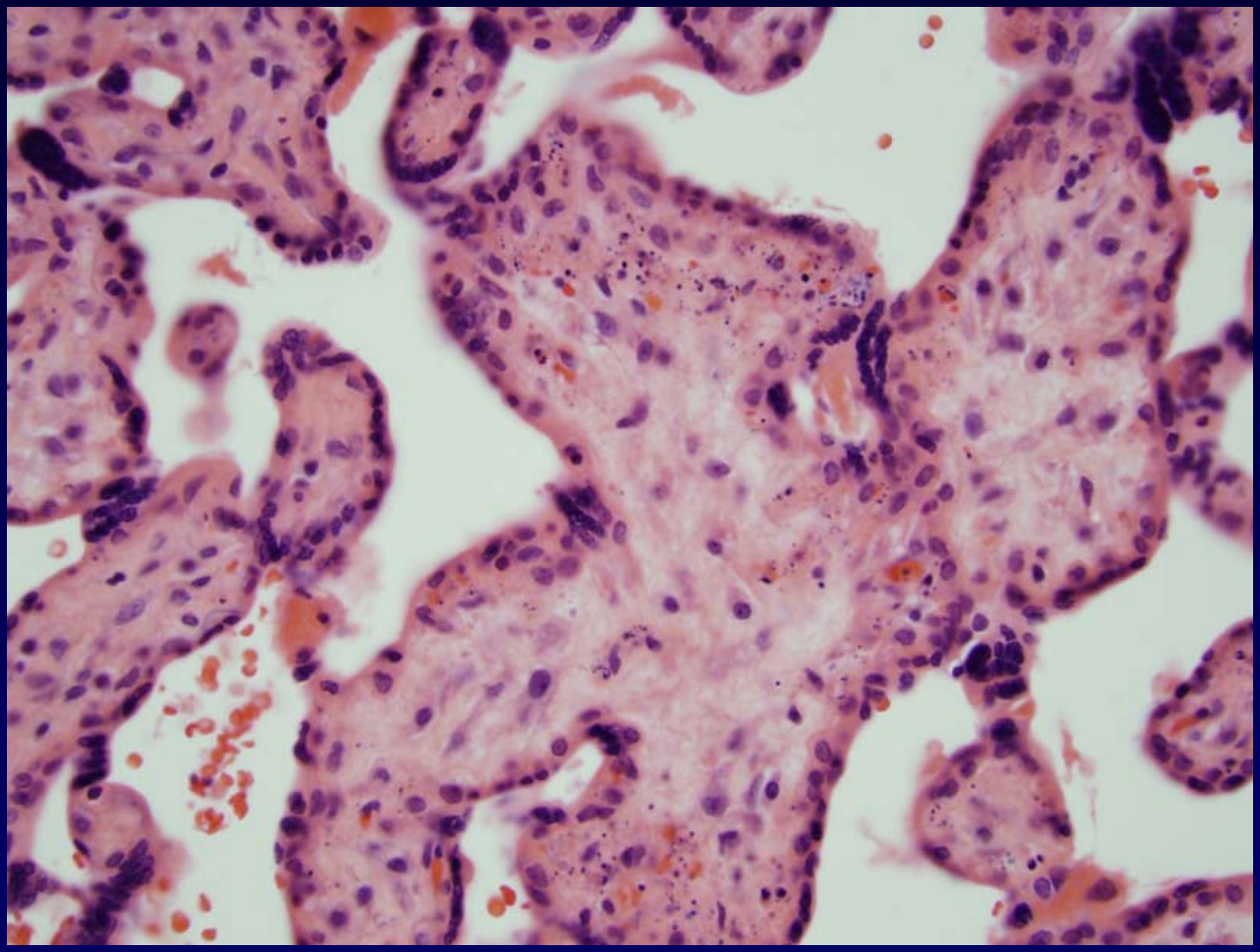
- Villous stromal-vascular karyorrhexis

  Three or more foci of two or more terminal villi with karyorrhexis of fetal cells – endothelium, stroma, nRBCs, or leukocytes

- Formerly termed hemorrhagic endovasculitis

Redline RW et al. Pediatr Dev Pathol 2004; 7:443-452

Villous Stromal-Vascular Karyorrhexis



Karyorrhexis in fetal vessels, fragmented red cells

Fetal Vascular Obstruction

Determine severity of uniformly avascular villi or villous stromal-vascular karyorrhexis:

- Any
- Severe

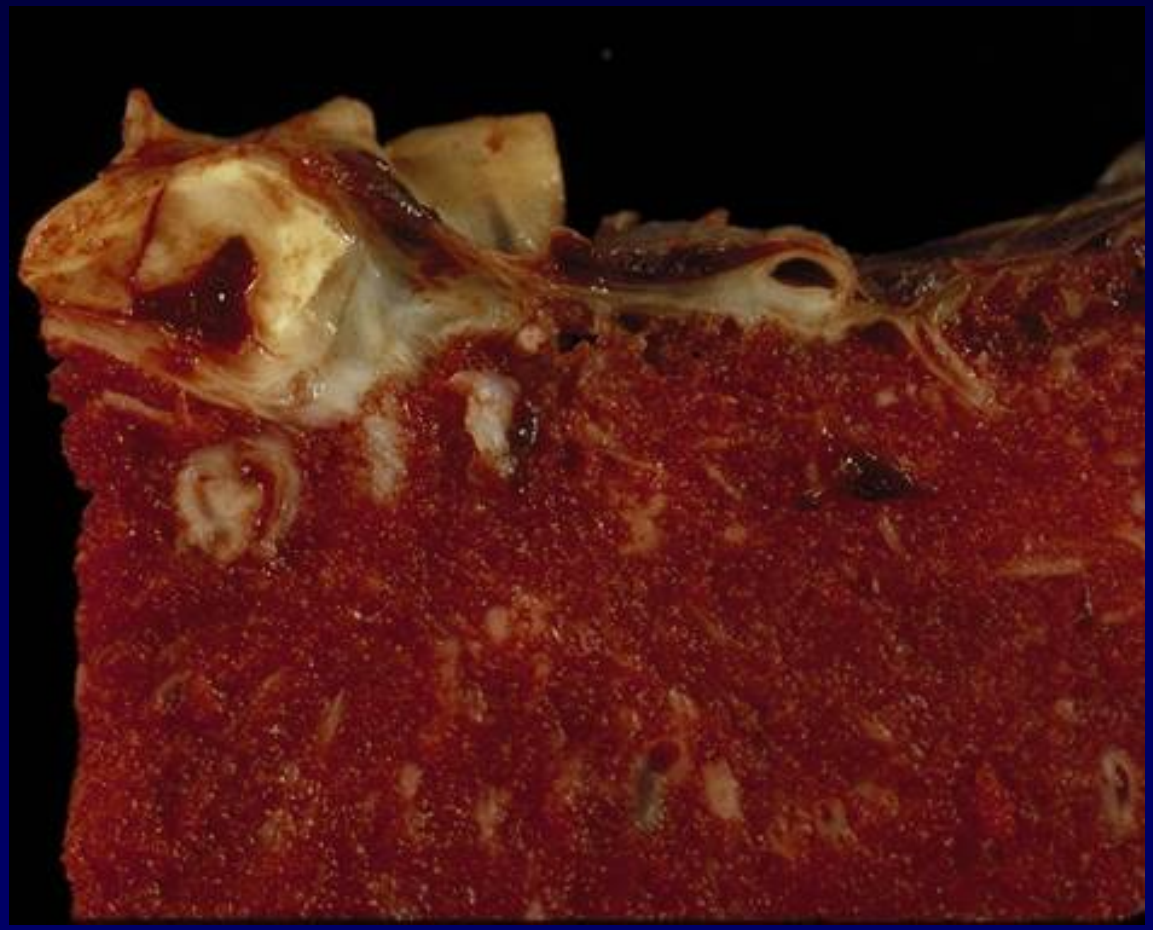
  More than two foci/average of 15 or more affected villi/slide

Redline RW et al. Pediatr Dev Pathol 2004;7:443-452

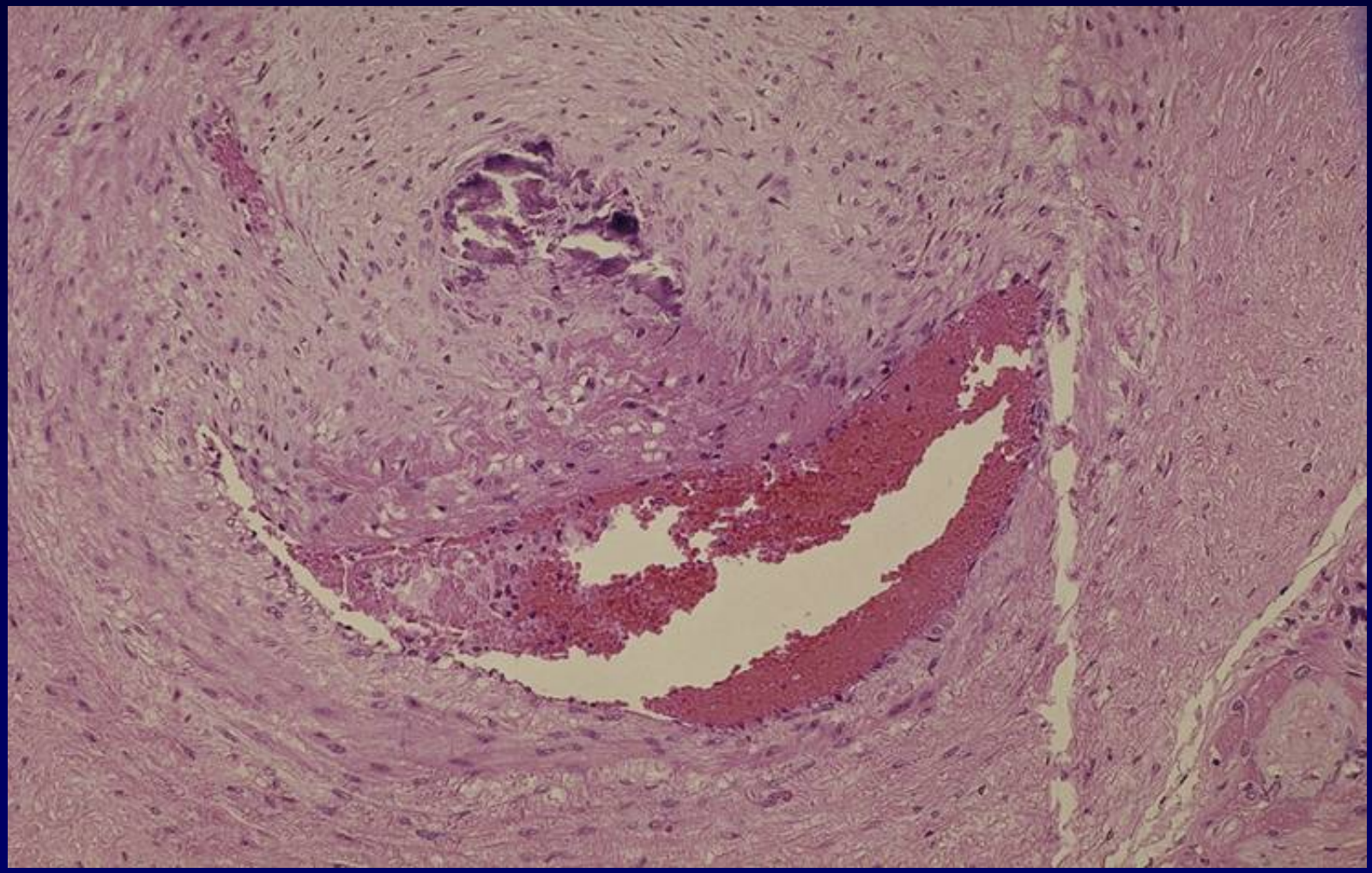
Fetal Vascular Obstruction

- Use the term fetal thrombotic vasculopathy only when there is severe fetal vascular obstruction

Chorionic Plate Vessel Thrombus with Calcification



Chorionic Plate Vessel Thrombus



Fetal Vascular Obstruction

Pathogenesis

- Stasis
- Hypercoagulability
- Vascular damage

Fetal Vascular Obstruction

Clinical Associations

- Maternal diabetes
- Maternal thrombophilia (but not fetal thrombophilia)
- Chorioamnionitis

Fetal Vascular Obstruction

- Cord abnormalities
  - Long cord
  - Velamentous insertion
  - Excess twisting
  - Nuchal cord

Fetal Vascular Obstruction

Consequences for fetus if extensive:

- Fetal growth restriction
- Chronic monitoring abnormalities
- Stillbirth
- Neurologic impairment
- Hepatic failure
- Vascular compromise involving kidneys, GI

Fetal Thrombotic Vasculopathy

84 consecutive perinatal autopsies

- 16 (19%) had avascular terminal villi
- extensive in all 16
- Involved 25 to 50% of placenta in 4
- 6 (37.5%) had fetal somatic thrombi
- 5/8 had coagulation abnormalities

Kraus FT, Archeen V Human Pathol 30:759, 1999

Fetal Thrombotic Vasculopathy

125 cases from children with neurologic deficits referred for litigation

- 4 vascular lesions significantly increased
  - Fetal thrombotic vasculopathy
  - VUE with obliterative fetal vasculopathy
  - Chorioamnionitis with fetal vasculitis
  - Meconium-associated vascular necrosis

Redline RW Am J Obstet Gynecol 2005; 192:452-7

Fetal Vascular Obstruction

- One or more of these seen in 51% of cases vs. 10% of controls
- 52% of CP patients had one of these lesions
- Cord abnormalities more common in infants with fetal thrombotic vasculopathy

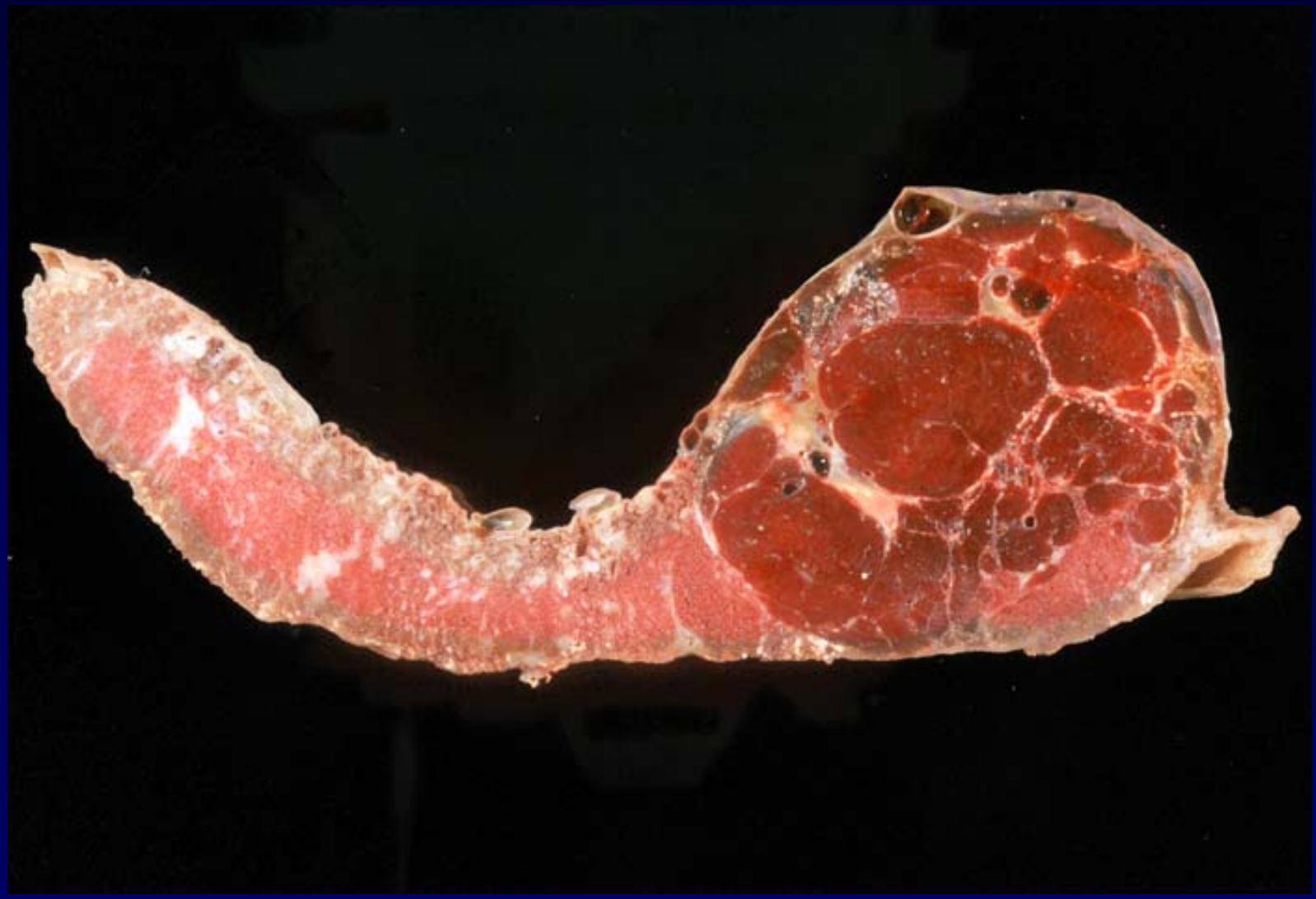
Redline RW Am J Obstet Gynecol 2005; 192:452-7
Redline RW Hum Pathol 2004;35:1494-8

Fetal Thrombotic Vasculopathy

Unanswered questions:

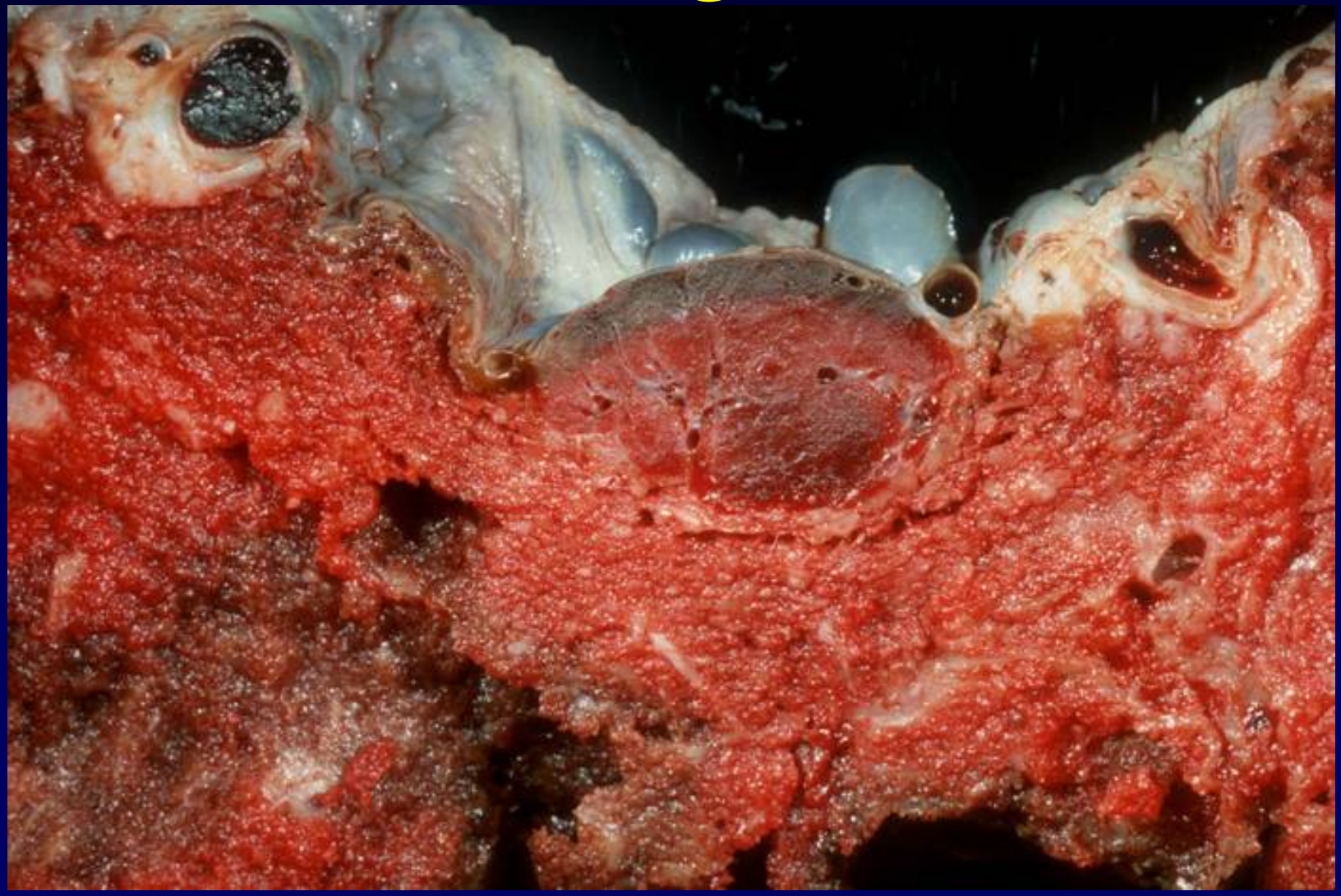
- Incidence from prospective data
- Predictive value
- Clinically significant amount
- Appropriate work up
- Role of treatment
- Pathogenesis

Chorangioma



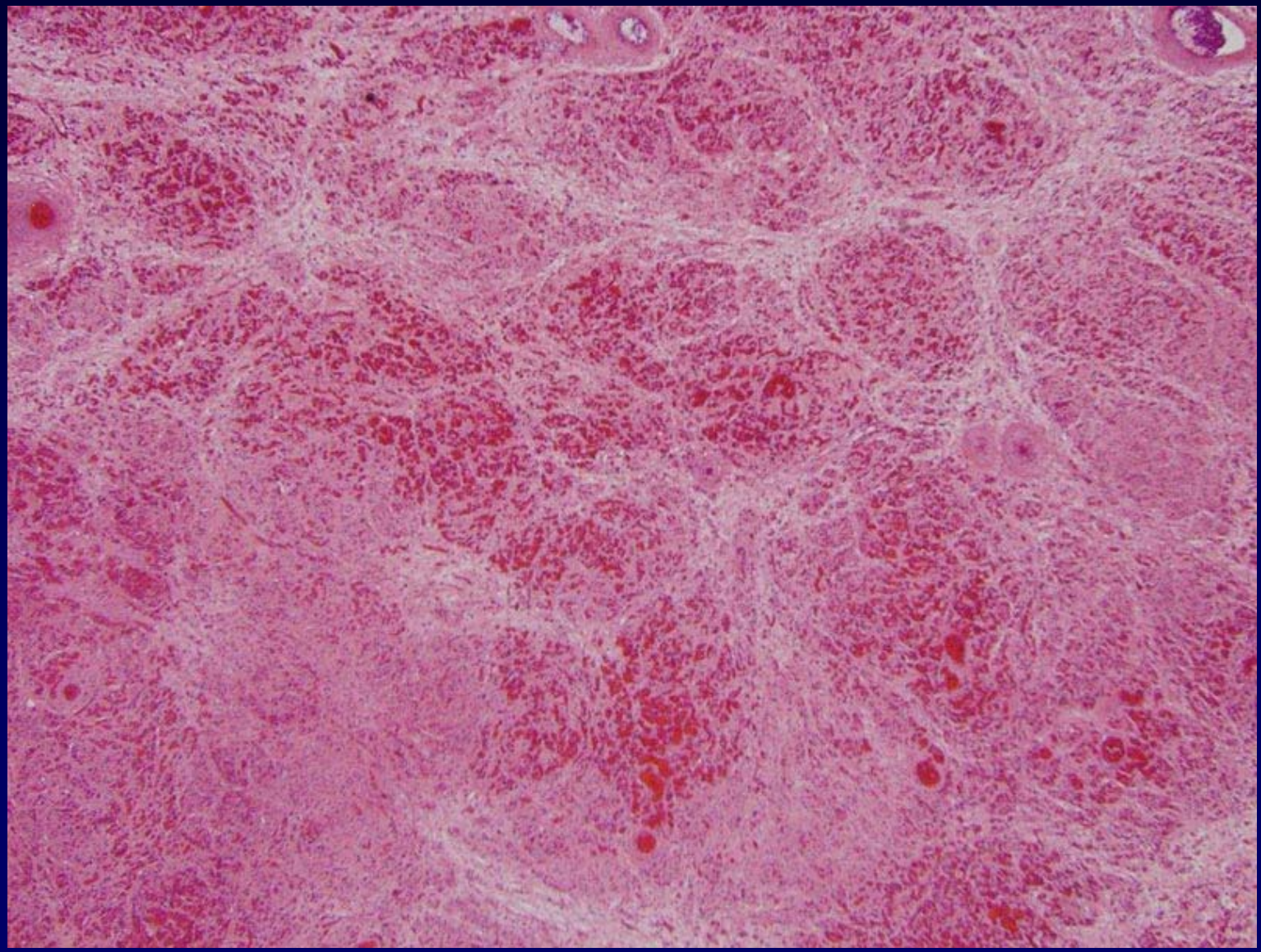
Chorangioma

Chorangioma

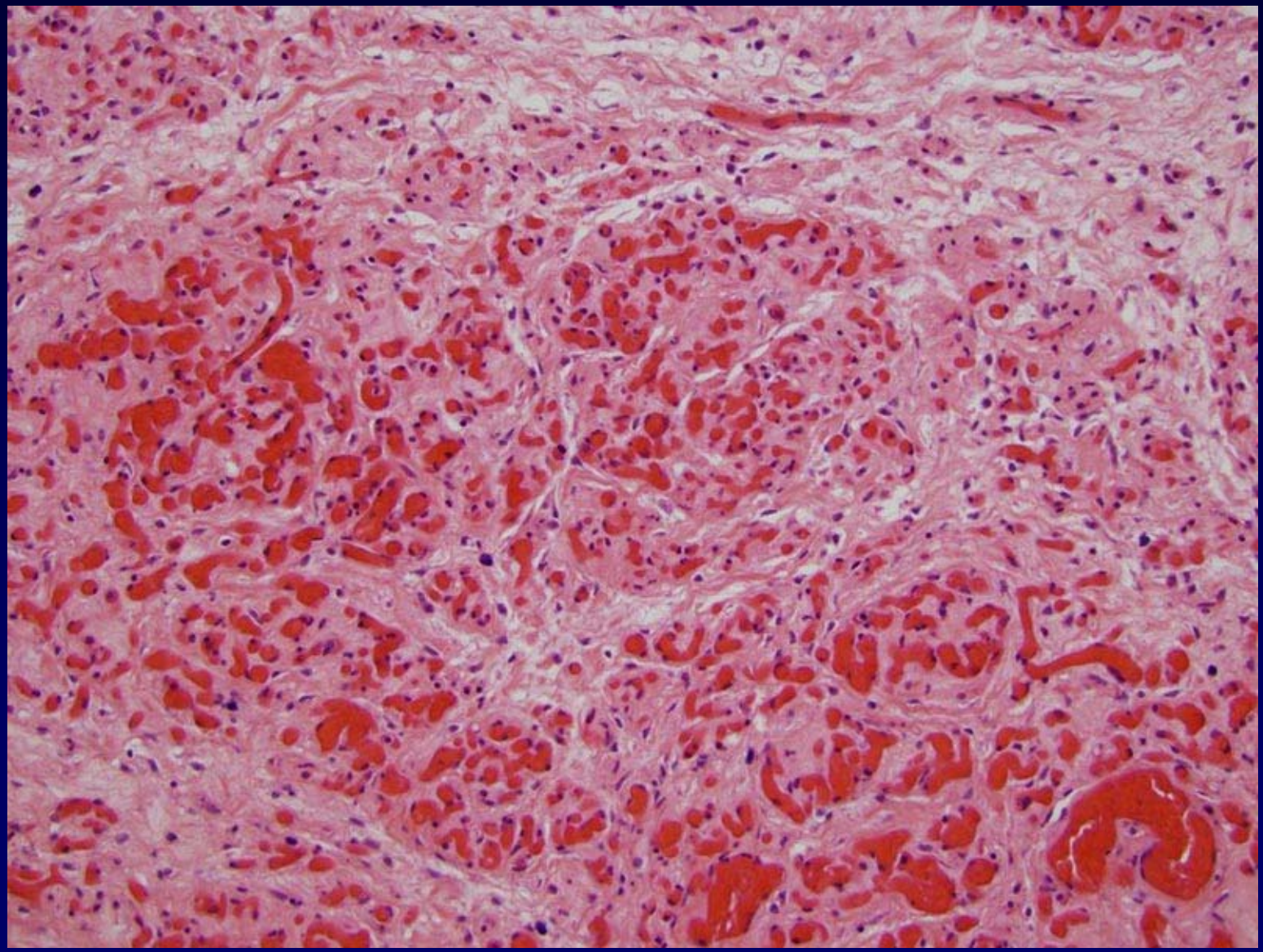


Small chorangiomas in fresh placenta may be subtle

Chorangioma



Chorangioma



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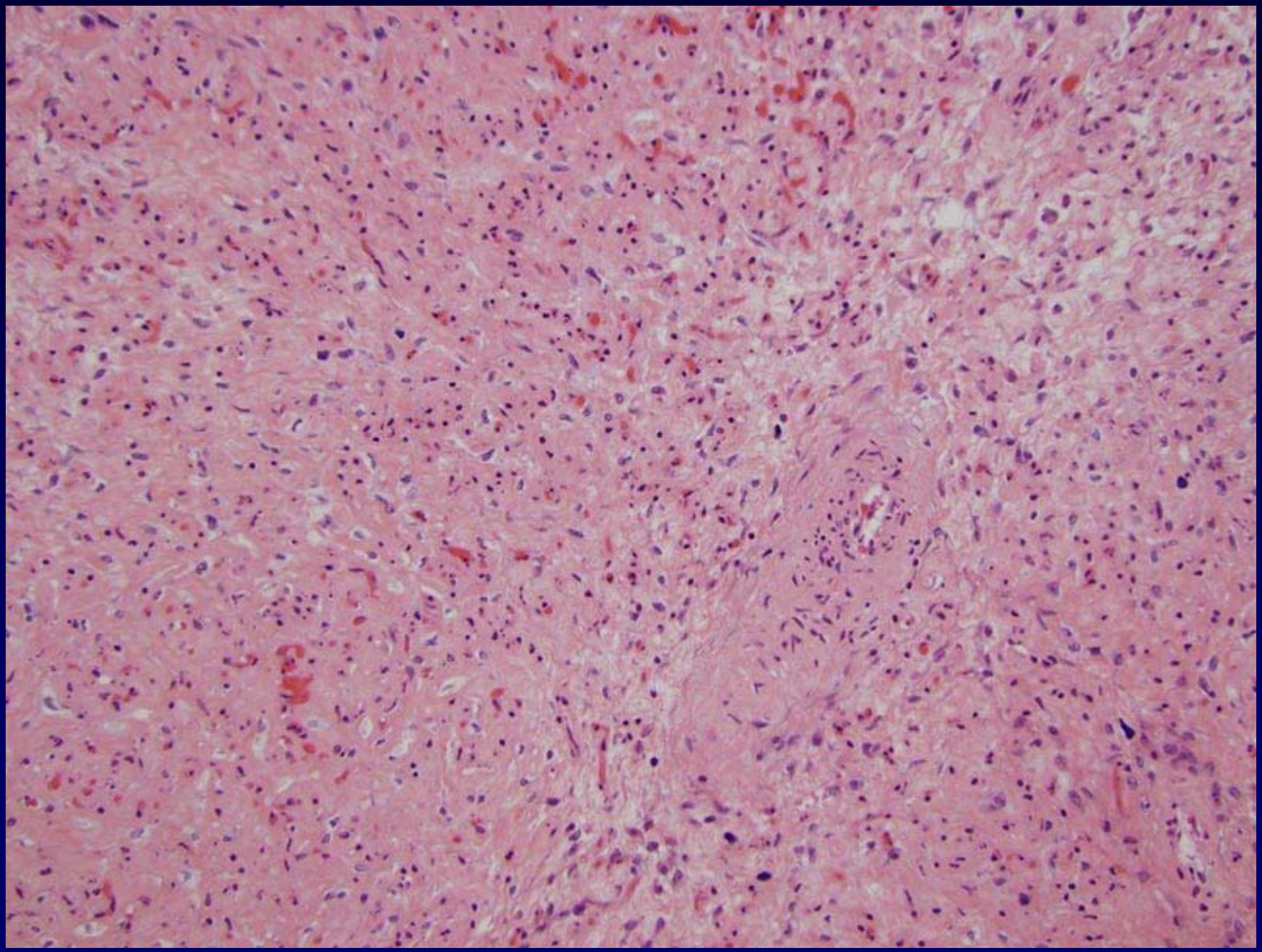
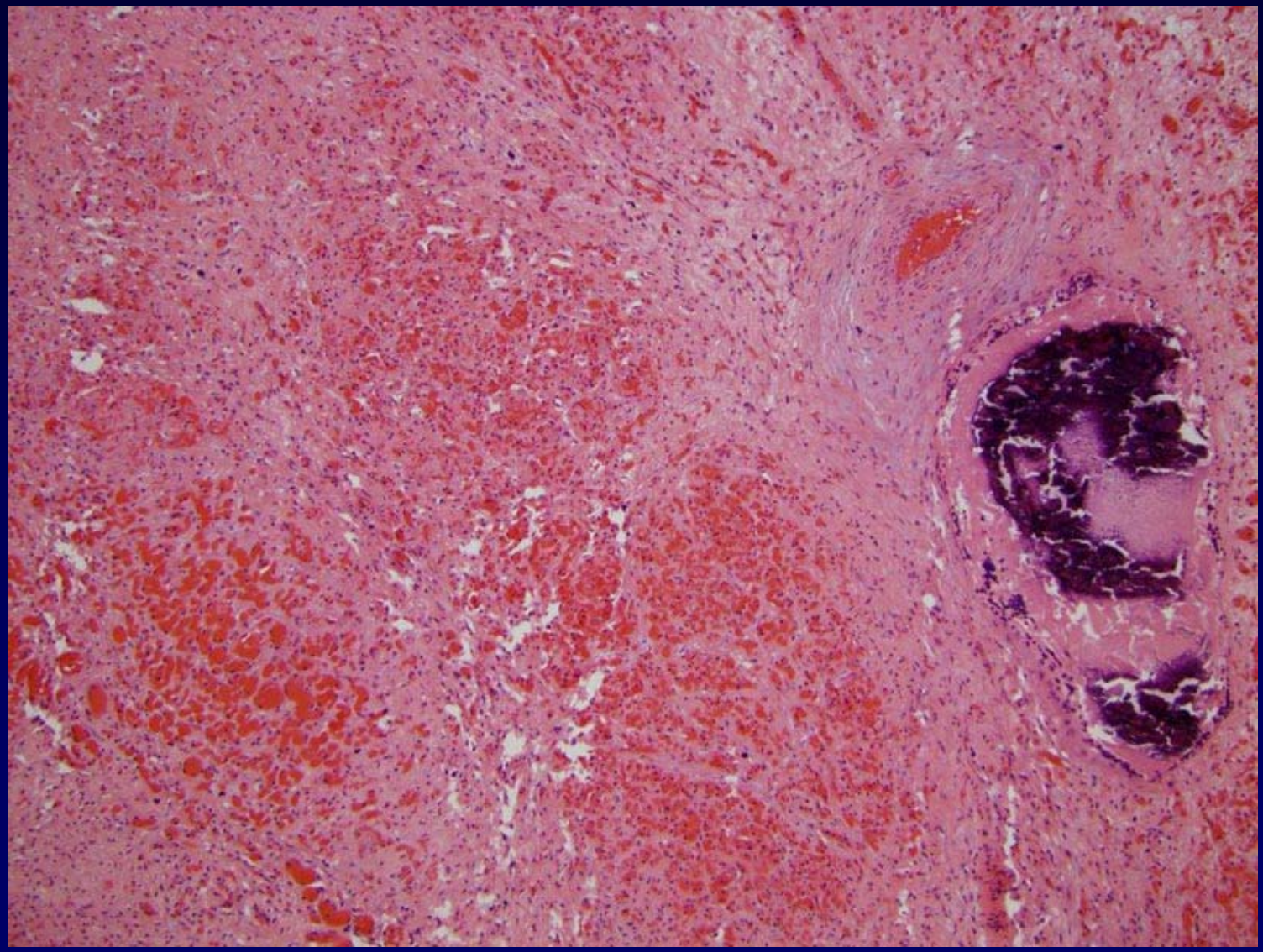


Chorangioma



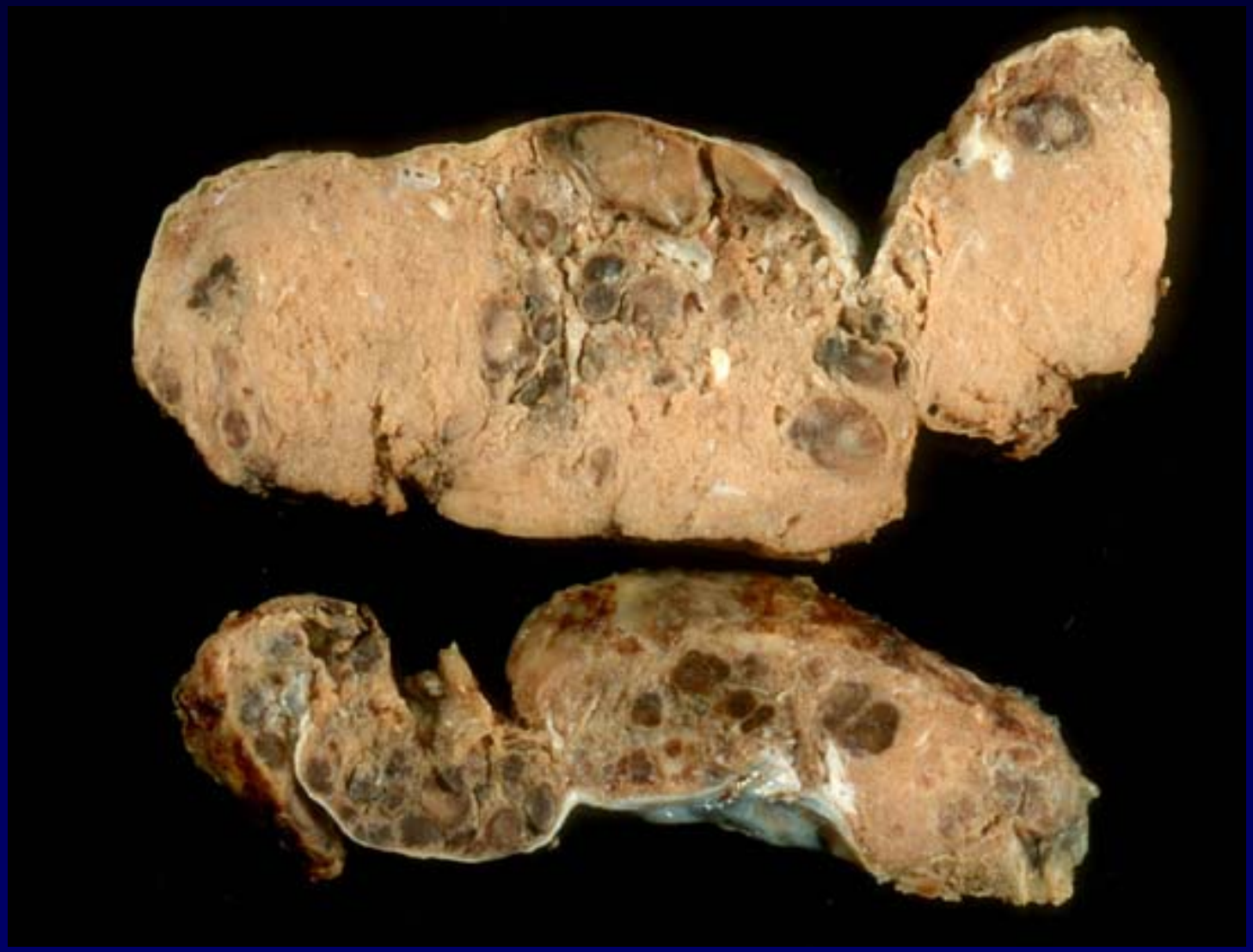
Chorangioma

- Small - see in 1% of placentas
- Large - 1:13,000 placentas
- Usually not clinically significant

Chorangioma

- If large or numerous may be associated with:
  - Cardiomegaly, hydrops fetalis
  - Polyhydramnios
  - Preterm delivery
  - Growth restriction
  - Anemia, thrombocytopenia
  - Neonatal death
- Recurrence
  - Rare, usually multiple, poor fetal outcome

Chorangioma



Chorangioma

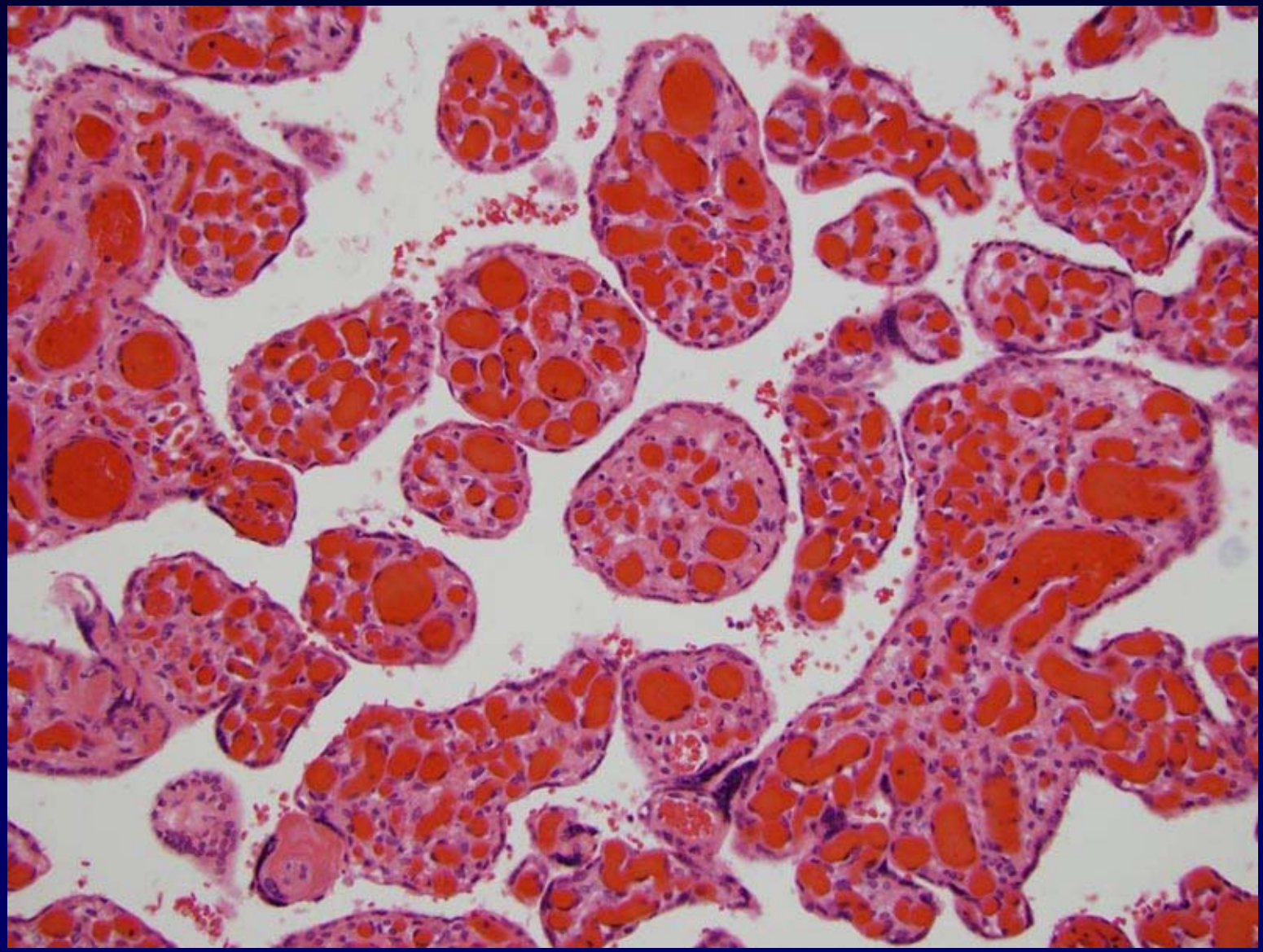
- Probably a hamartoma rather than a neoplasm
- Pathogenesis
  - Left to right shunt causing heart failure
  - Returns low oxygen blood to fetus

Chorangiosis

Definition:

more than 10 capillaries per terminal villus in 10 terminal villi in at least three different areas of the placenta

Chorangiosis



Chorangiosis

- Prevalence is about 5%
- Typically see in term gestations
- Associated pathologic findings
  - Large placental size
  - Delayed villous maturation
  - Chronic villitis
  - Ischemic lesions

Chorangiosis

Associated clinical findings

- Congenital anomalies
- Maternal diabetes
- Maternal anemia
- Maternal smoking
- Twin gestation
- Delivery at high altitude

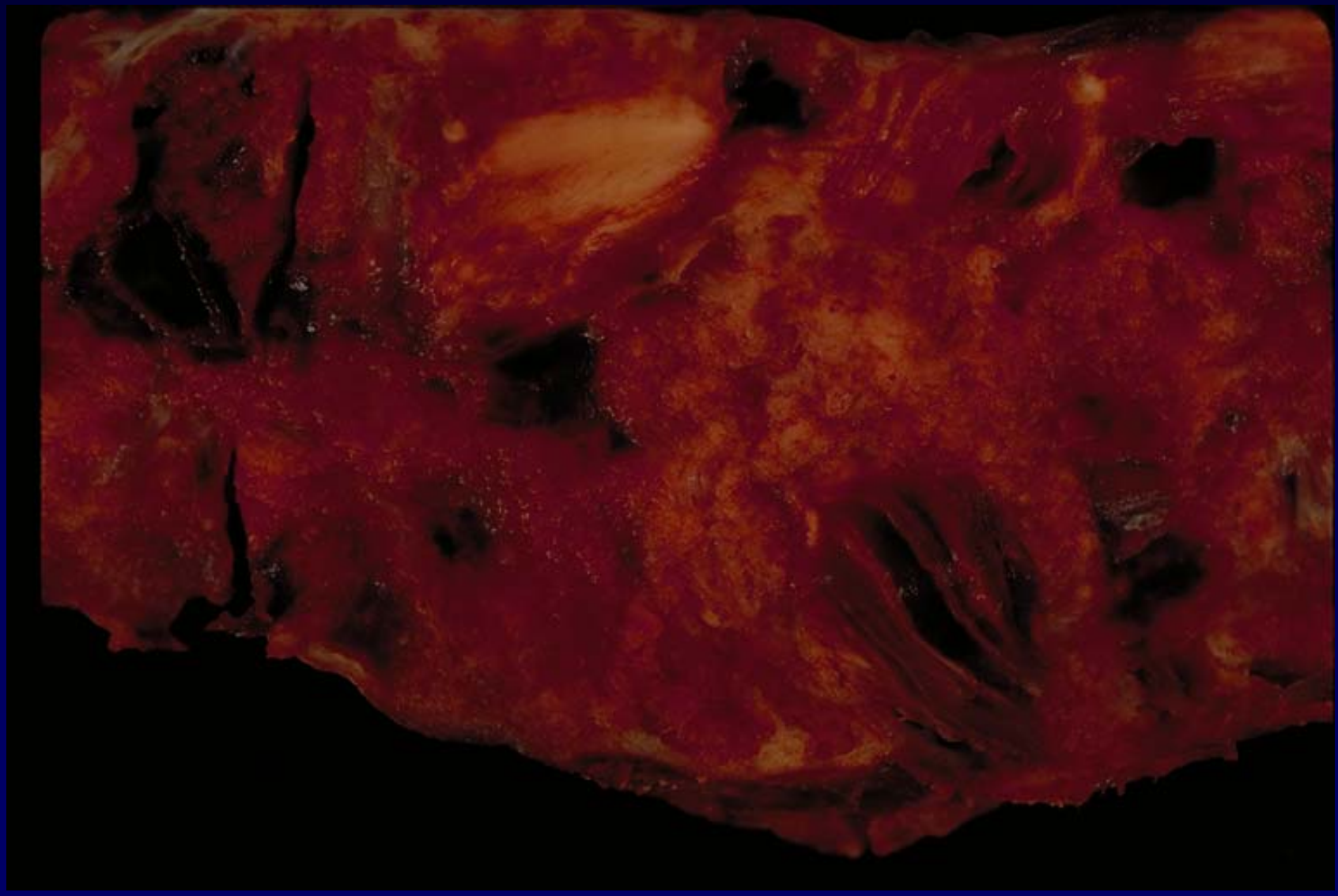
Chorangiosis

Pathogenesis theories

Capillaries proliferate in response to :

- Hypoxia
- Increased pressure from venous obstruction in cord or fetal heart
- Cytokines released from inflammatory cells

1



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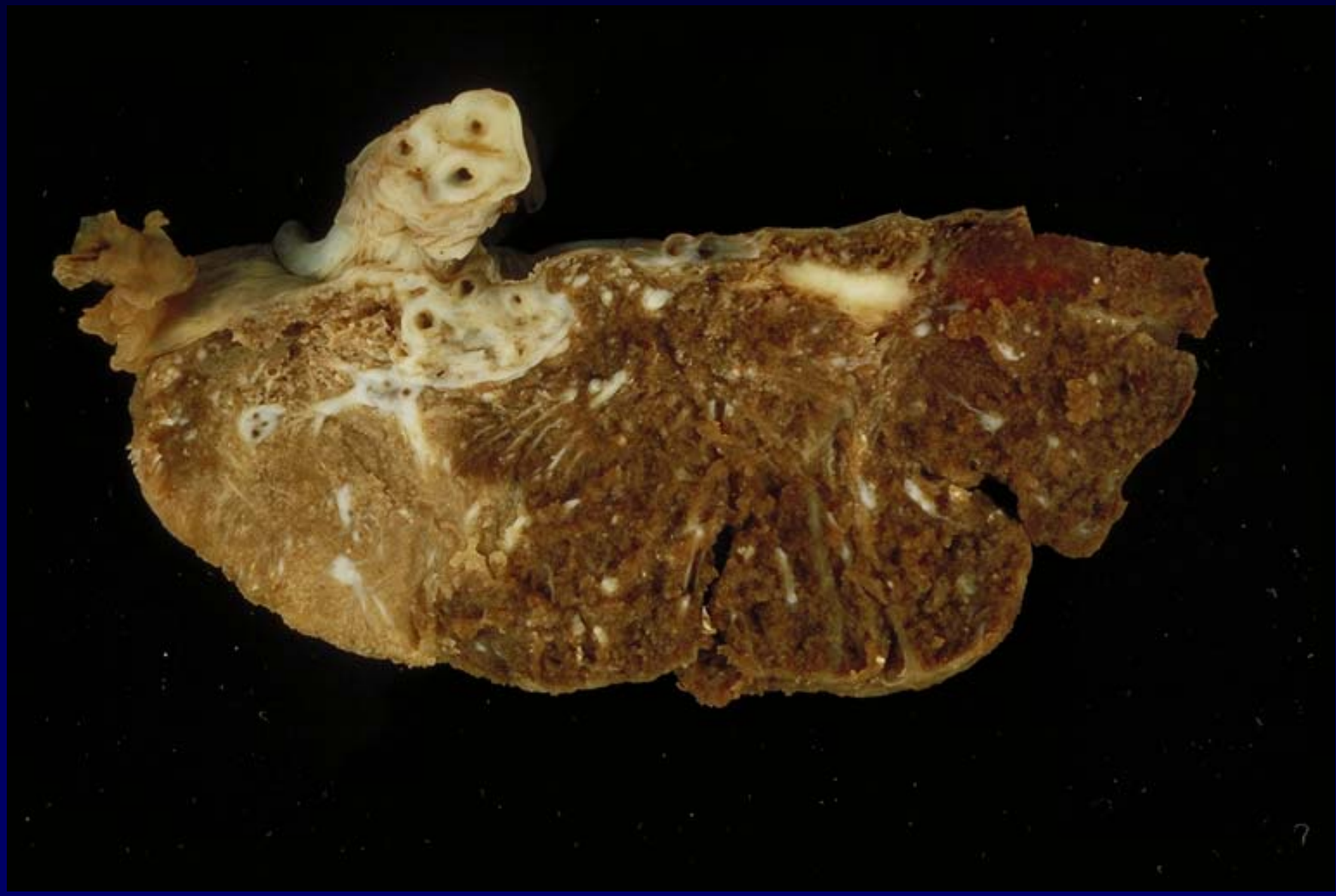

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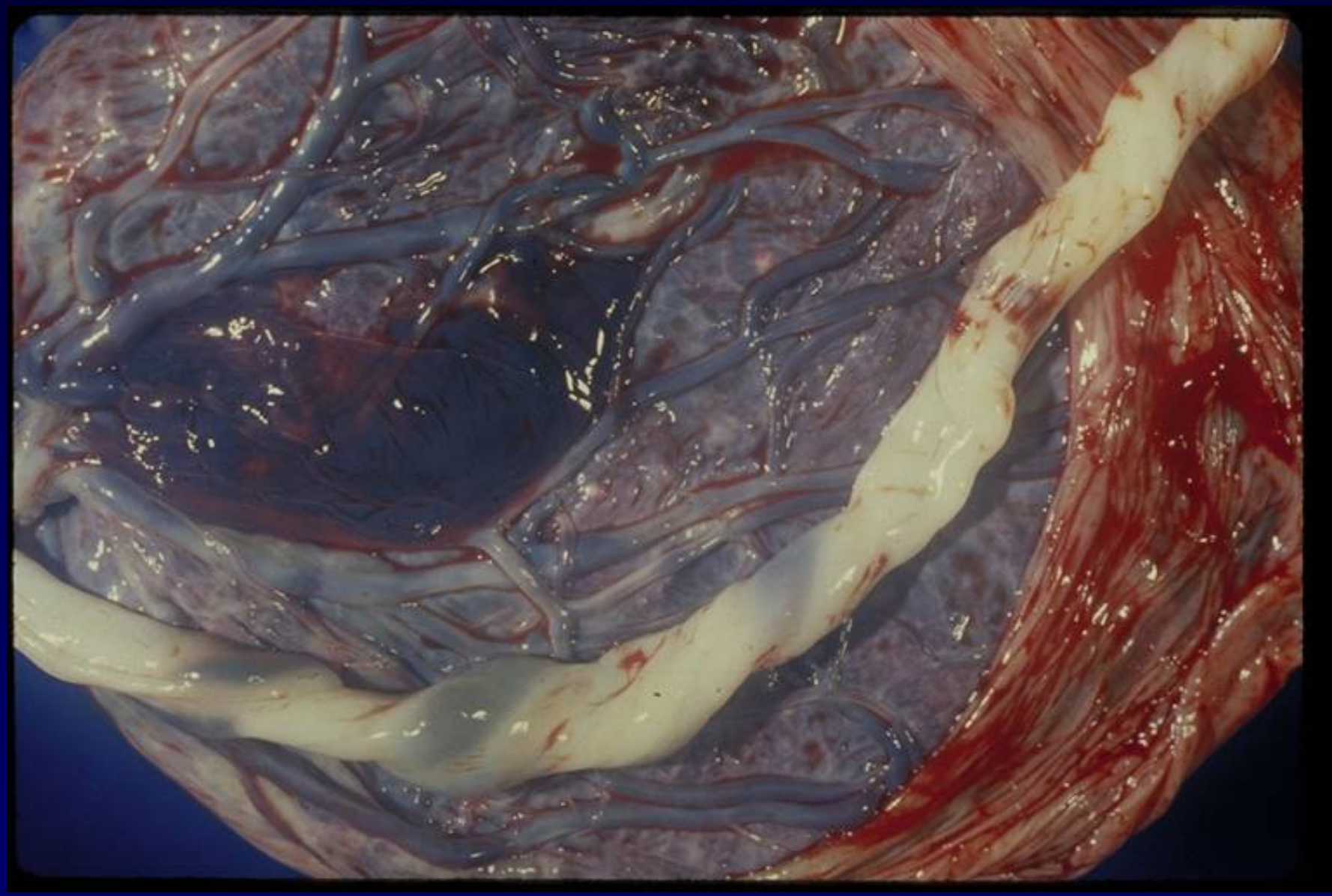

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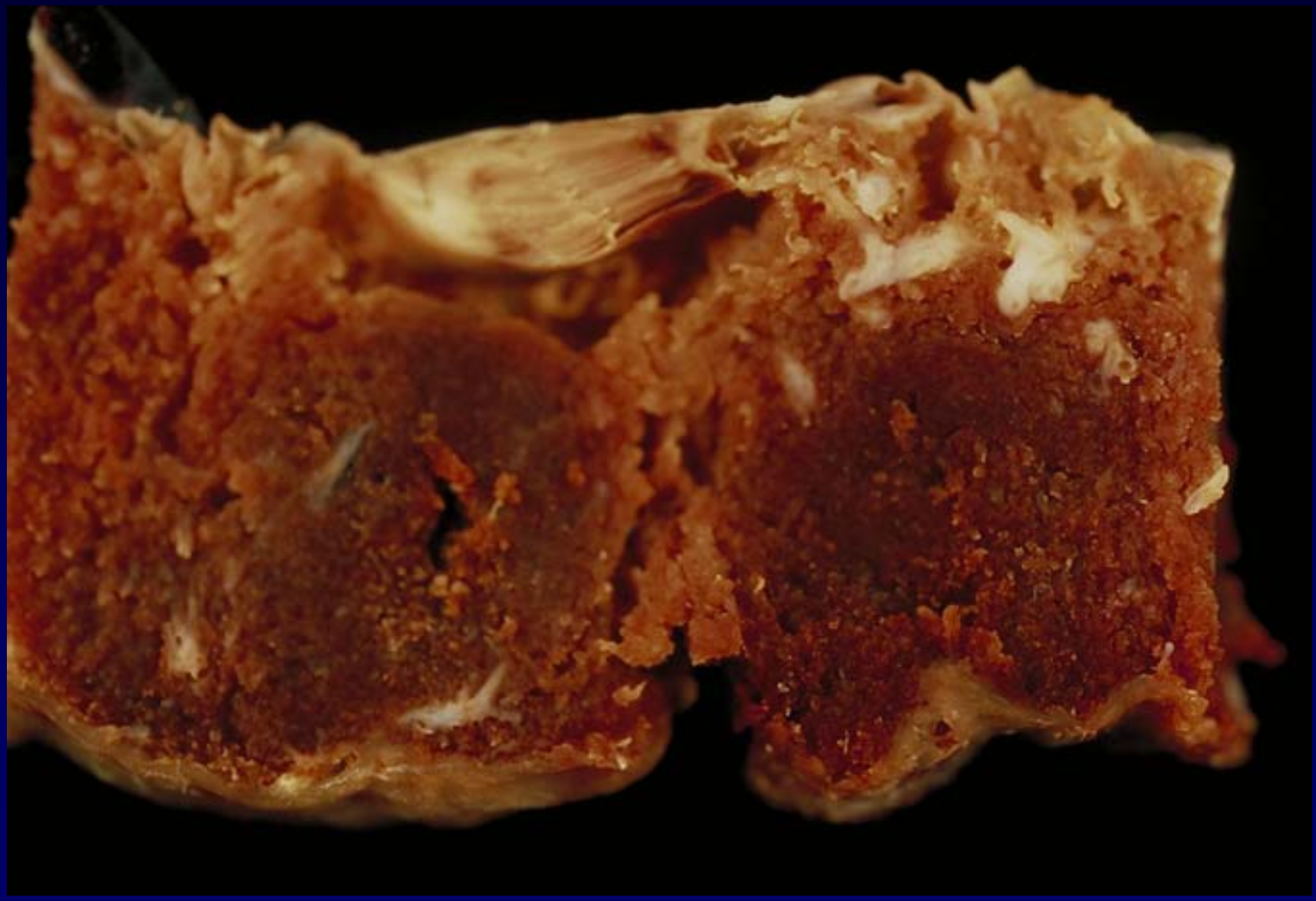

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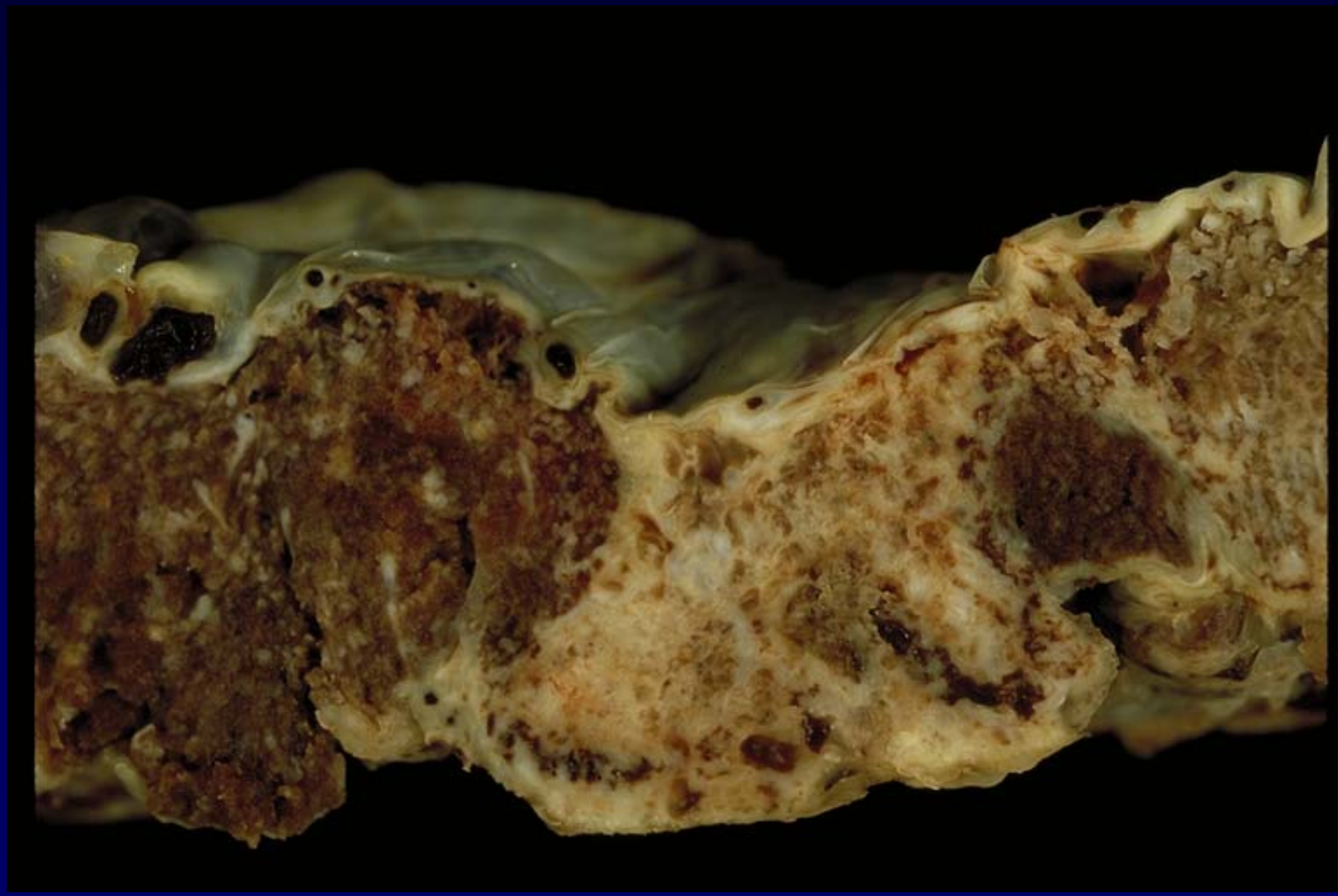

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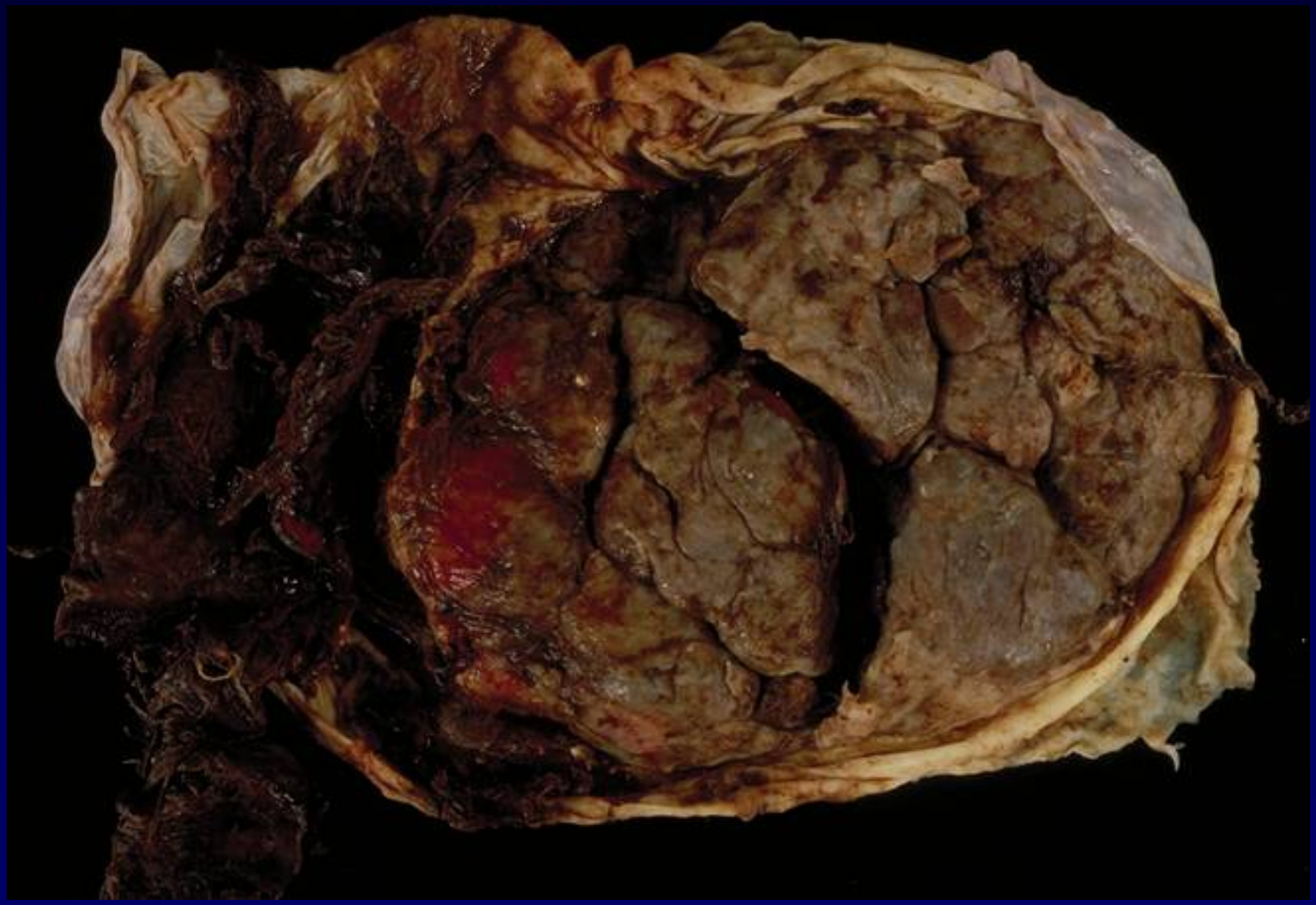

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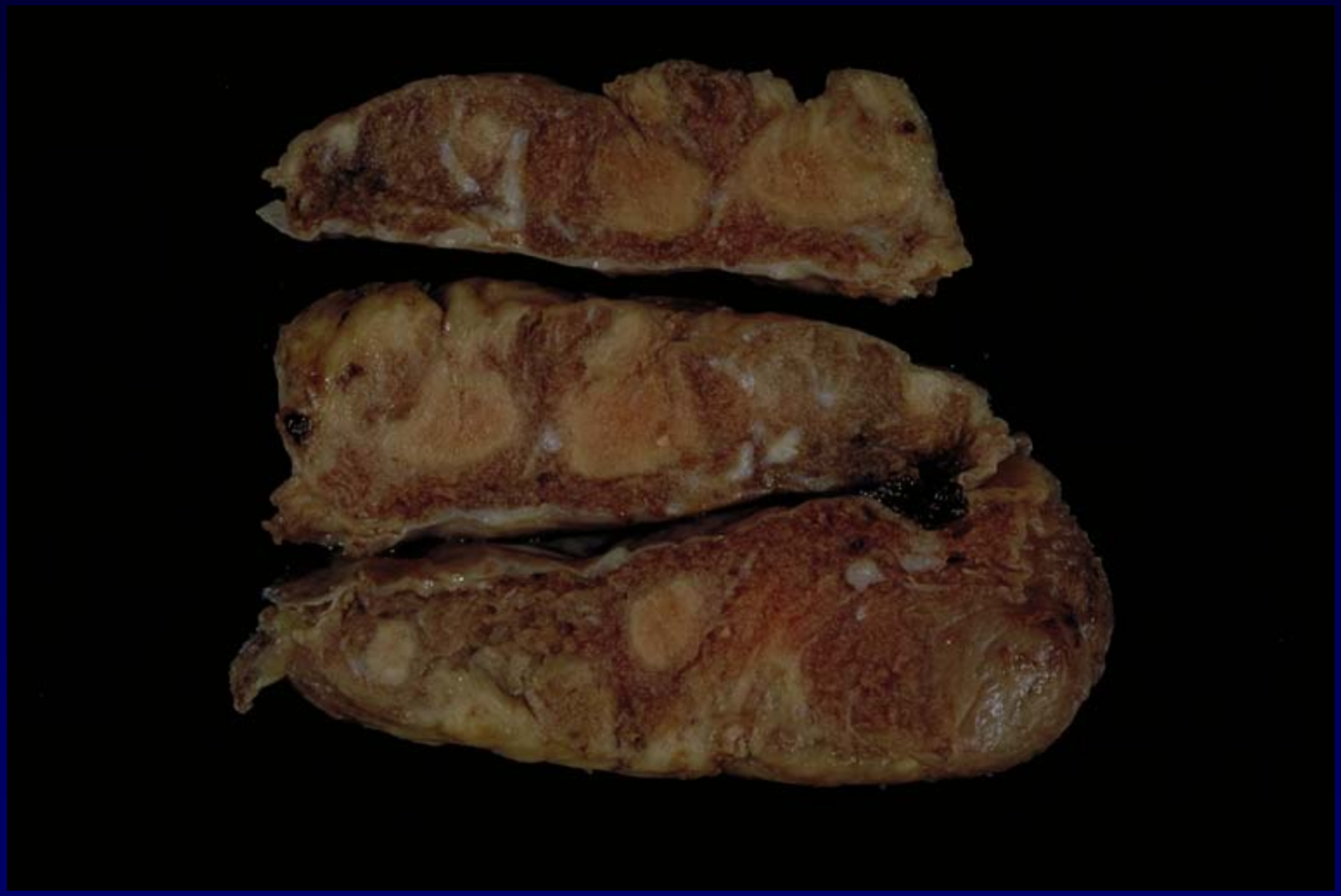


Placenta in Maternal Diseases

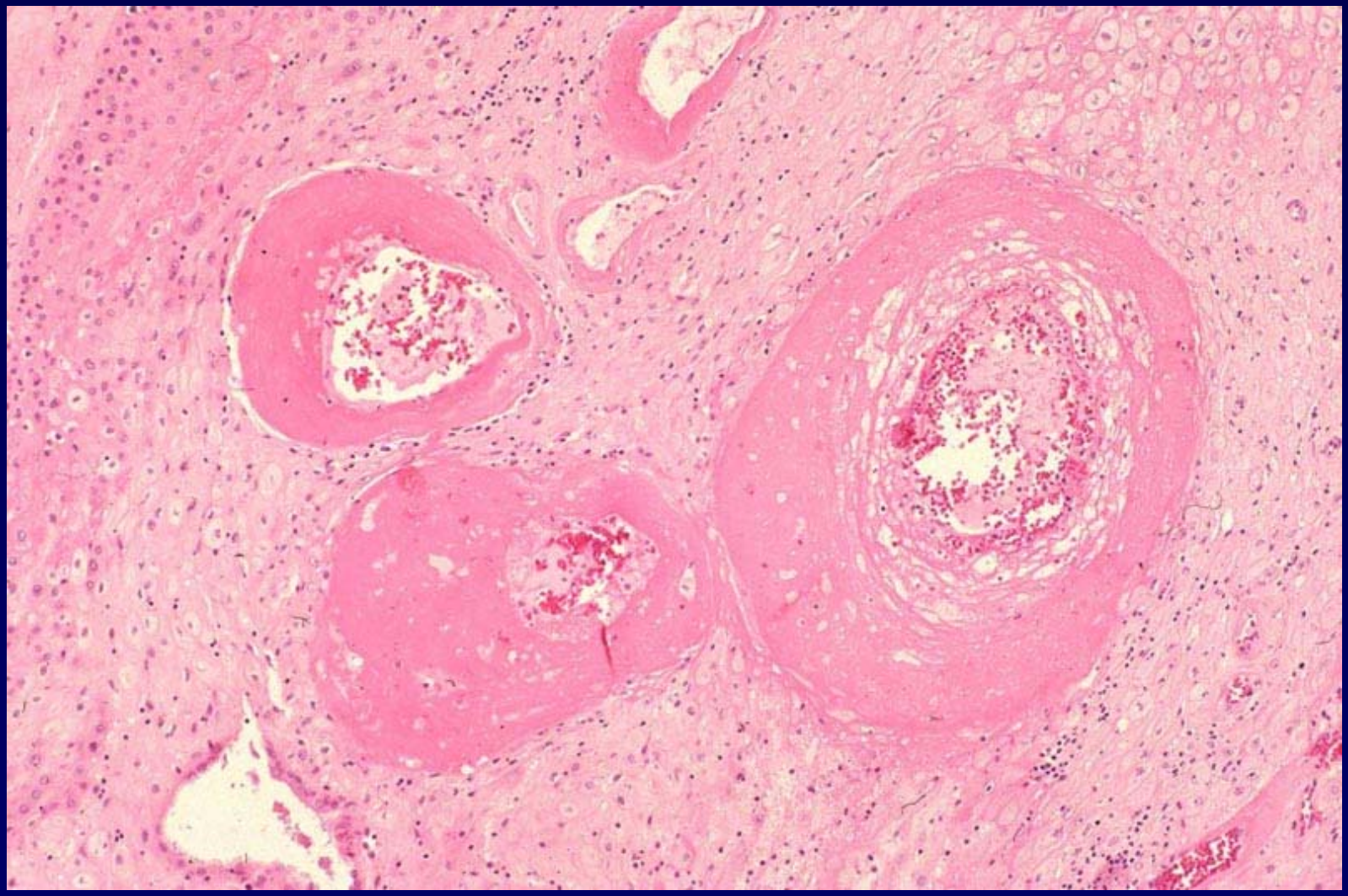
- Preeclampsia
- Lupus, anti-phospholipid antibody syndrome
- Maternal thrombophilic disorders
- Diabetes

Common findings: small placenta, maternal vascular changes, growth restricted infant

Case 3

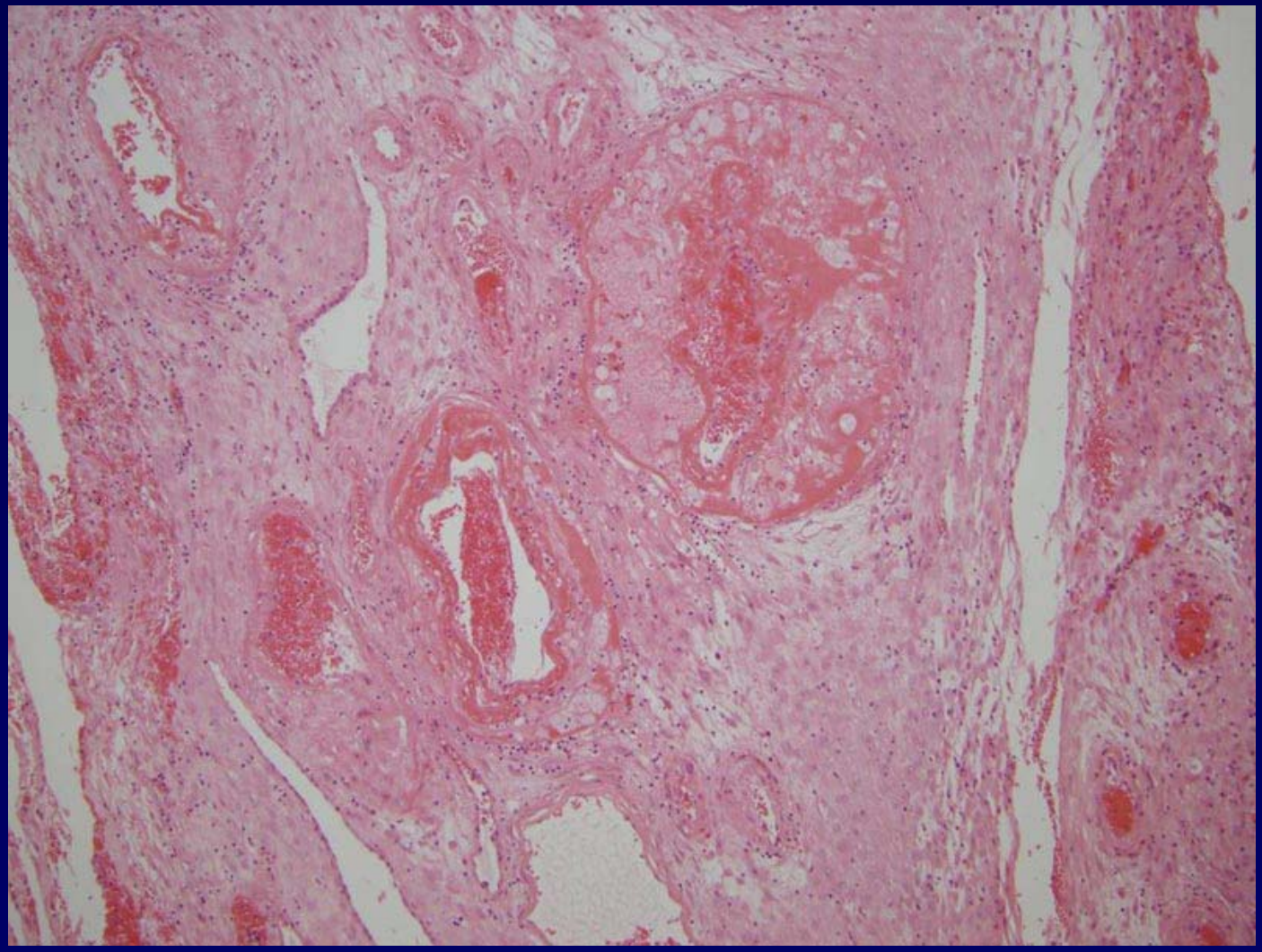
This 27 year old G2P1 woman was admitted at 28 weeks gestation for severe oligohydramnios, pregnancy-induced hypertension and severe intrauterine growth restriction. The infant was delivered two weeks later because of decreased fluid volume, lack of growth and incipient fetal jeopardy.

Acute Atherosis



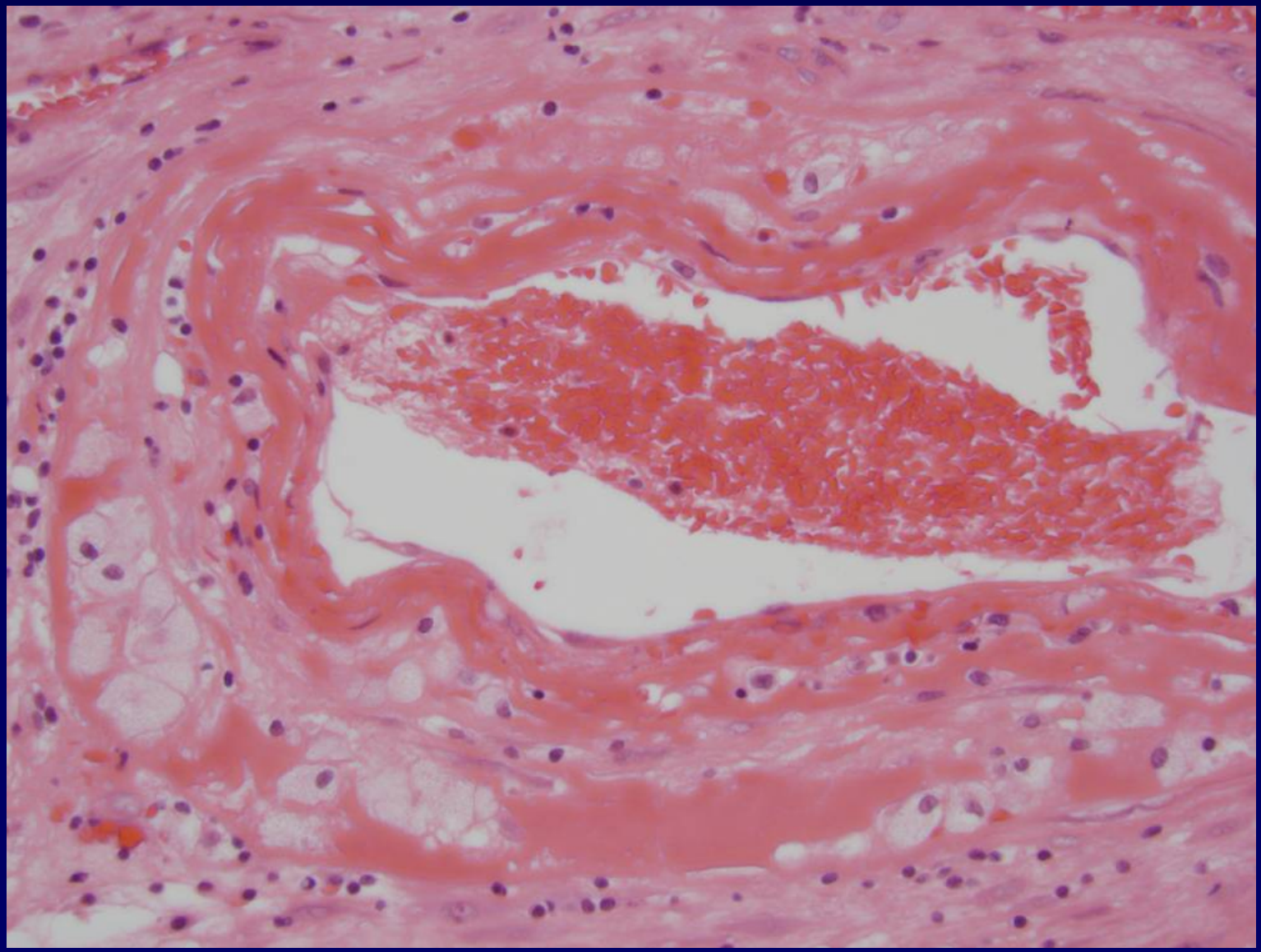
Prominent fibrinoid necrosis, very narrow lumens

Acute Atherosis

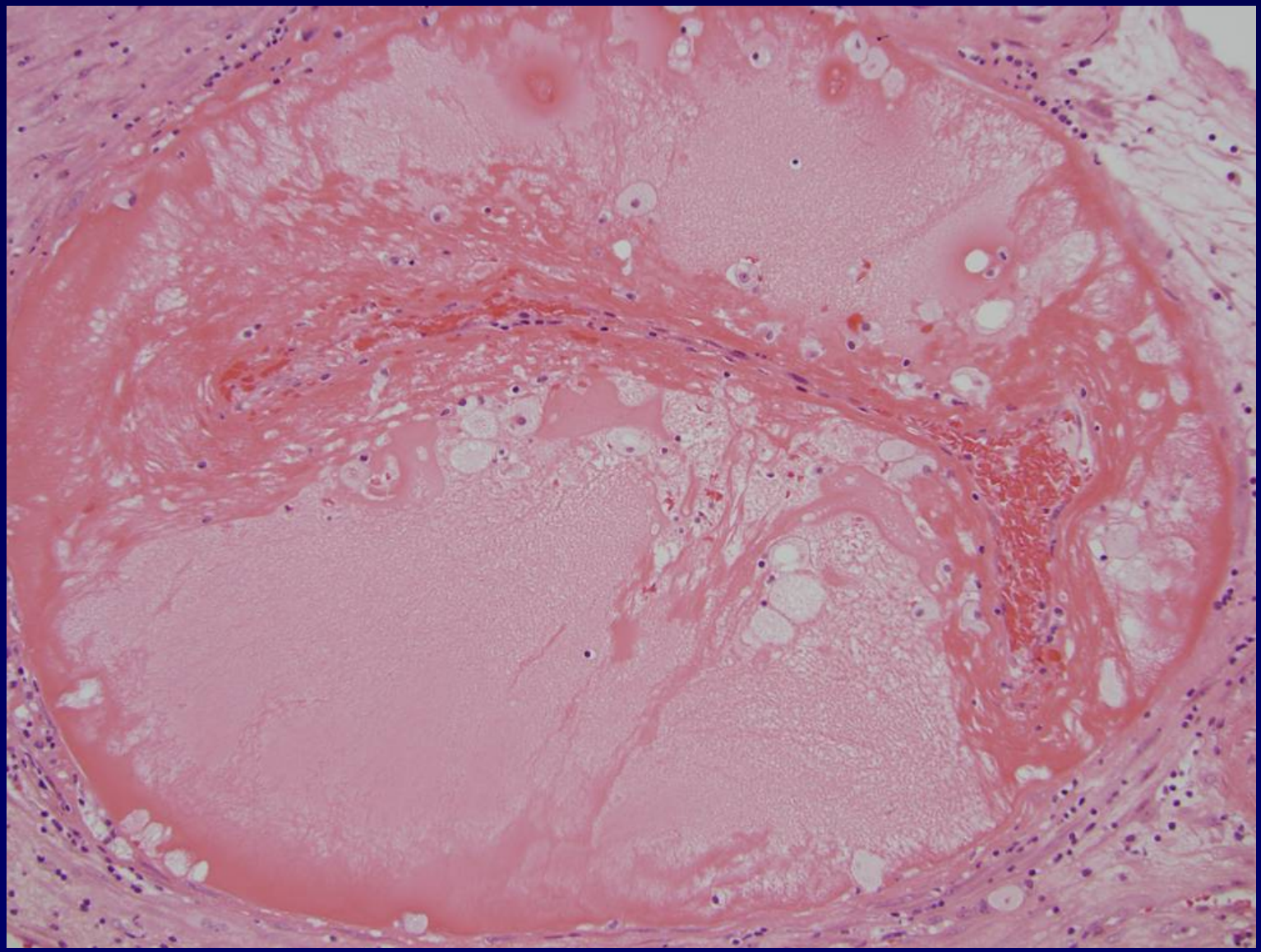


Fibrinoid necrosis, foamy macrophages

Acute Atherosis



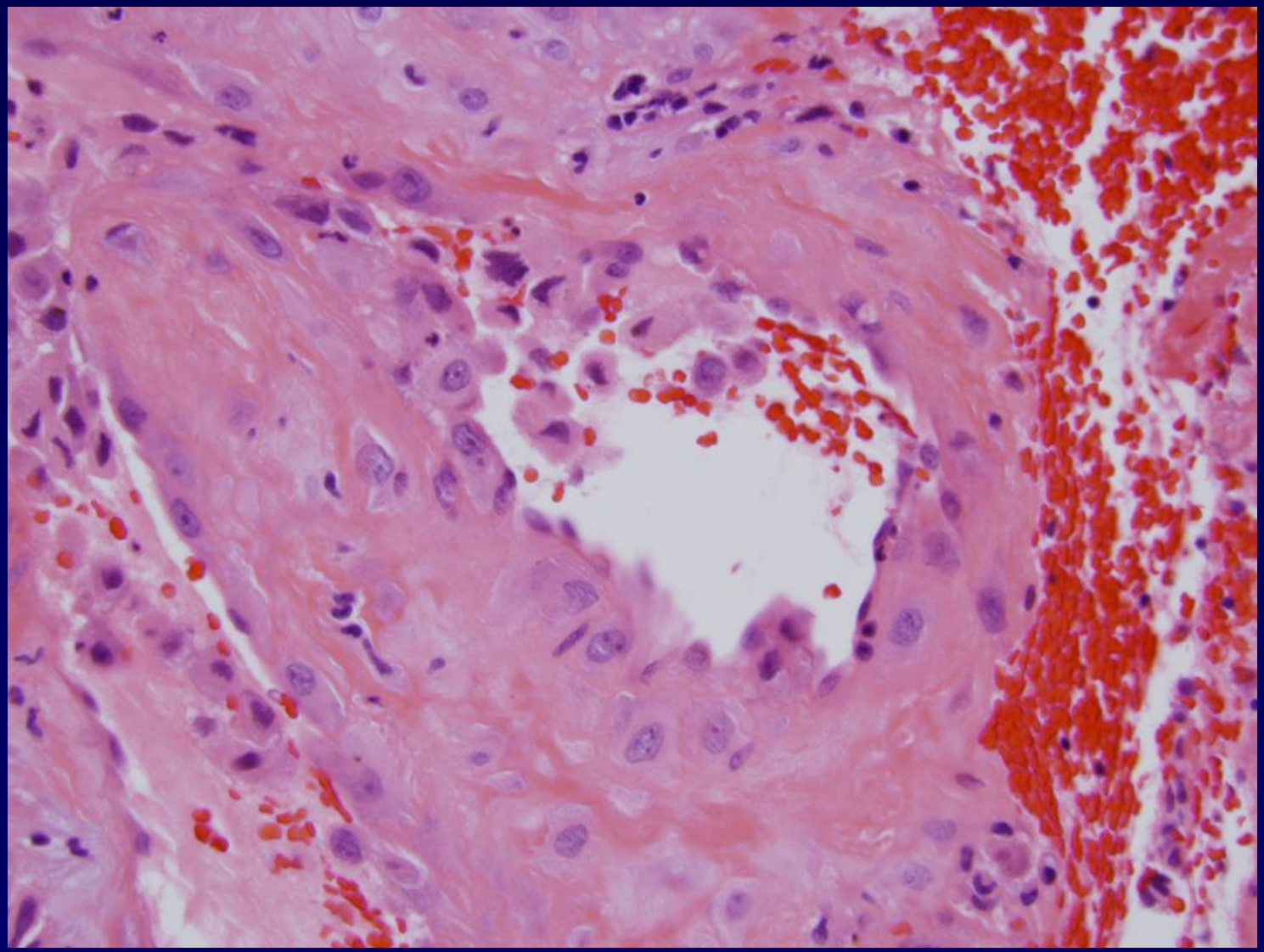
Acute Atherosis



Acute Atherosis

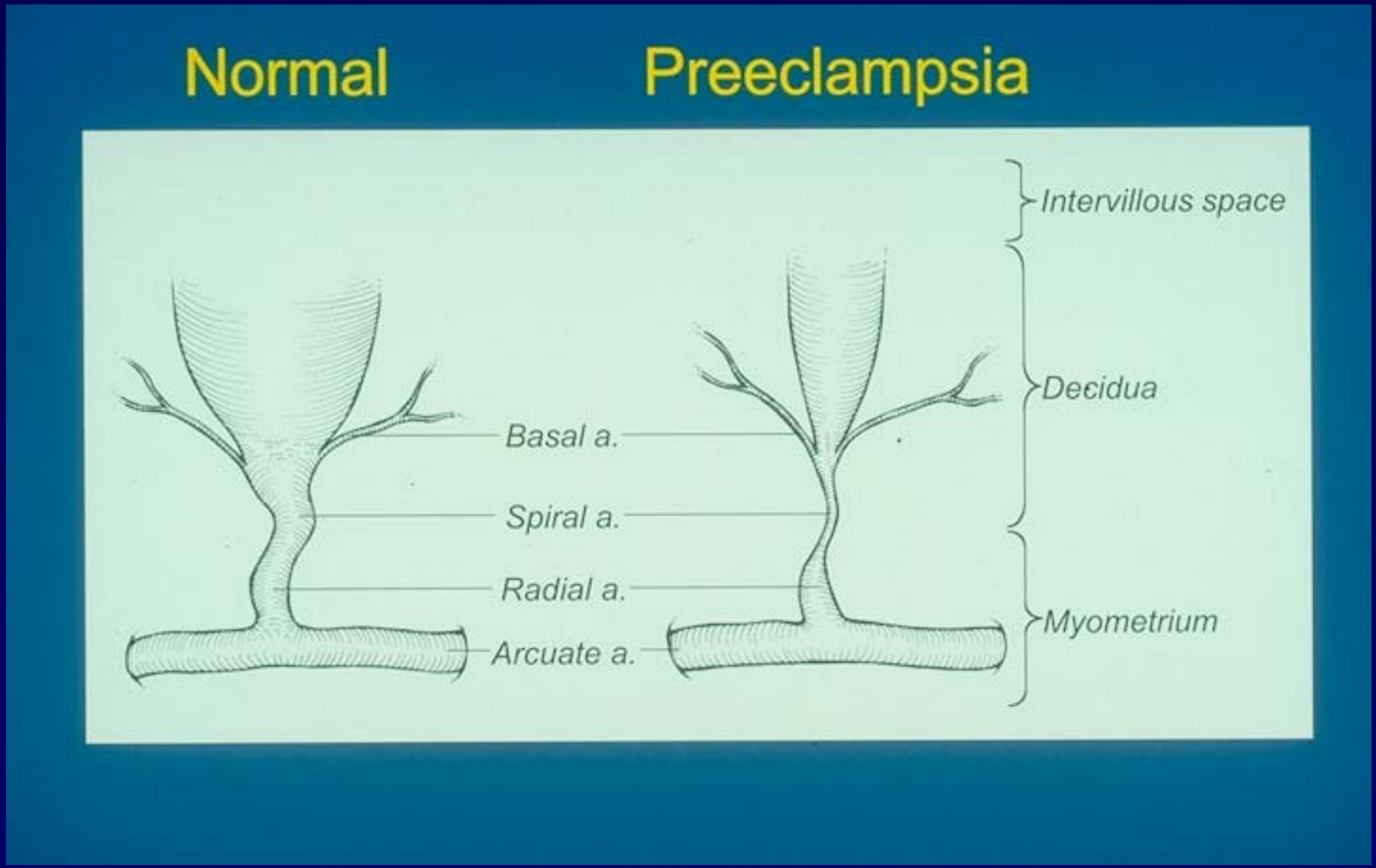
- Preeclampsia
  - Presence related to severity
  - Only see in ~ 50% with extensive sampling
- Idiopathic intrauterine growth restriction
- Small for gestational age infants
- Collagen vascular diseases

Normal Vascular Remodeling



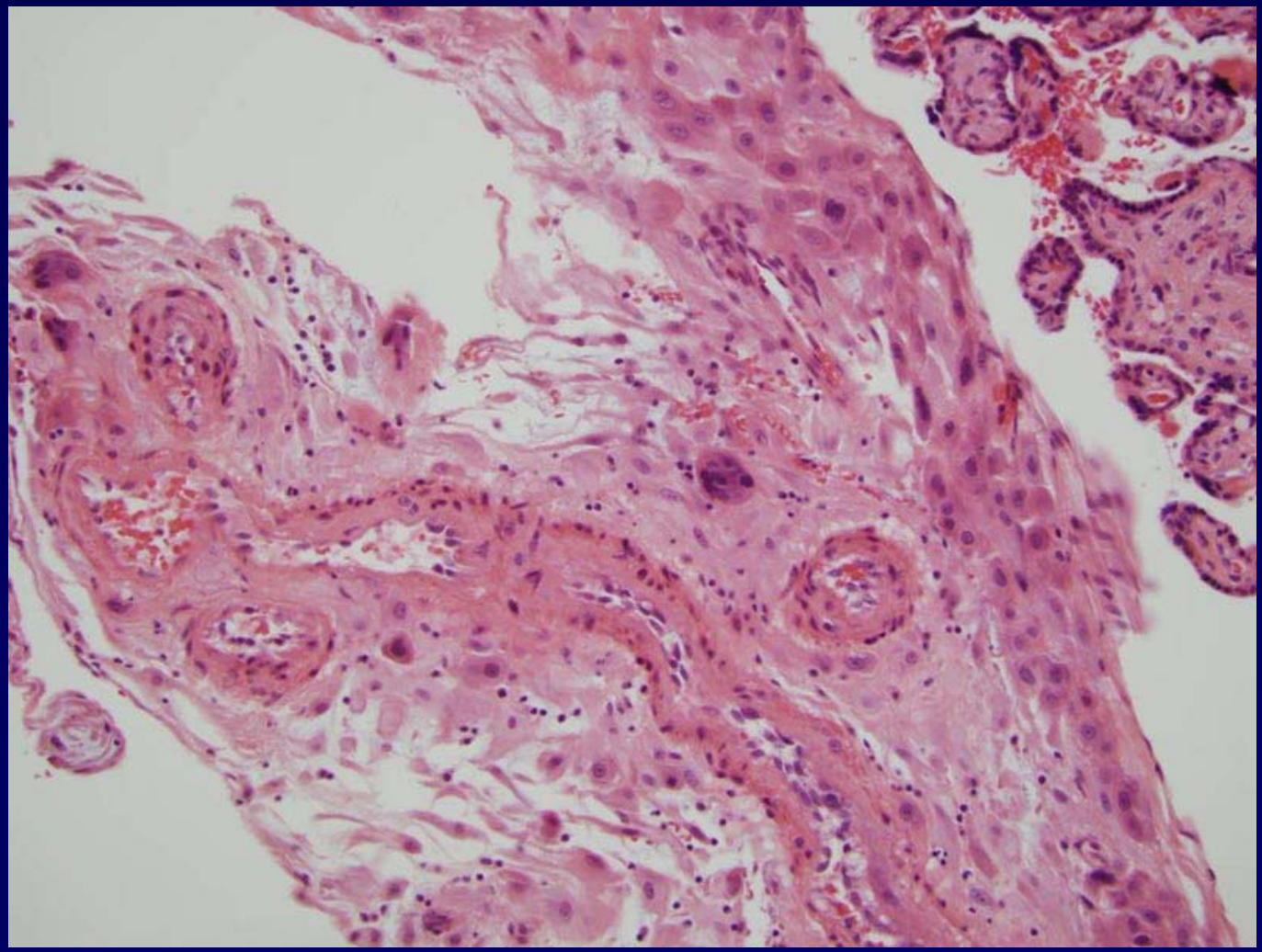
Normal Vascular Remodeling

- Replacement of smooth muscle and elastic by fibrinoid material
- Vessels become flaccid, low resistance tubes
- Increases blood flow 10-fold



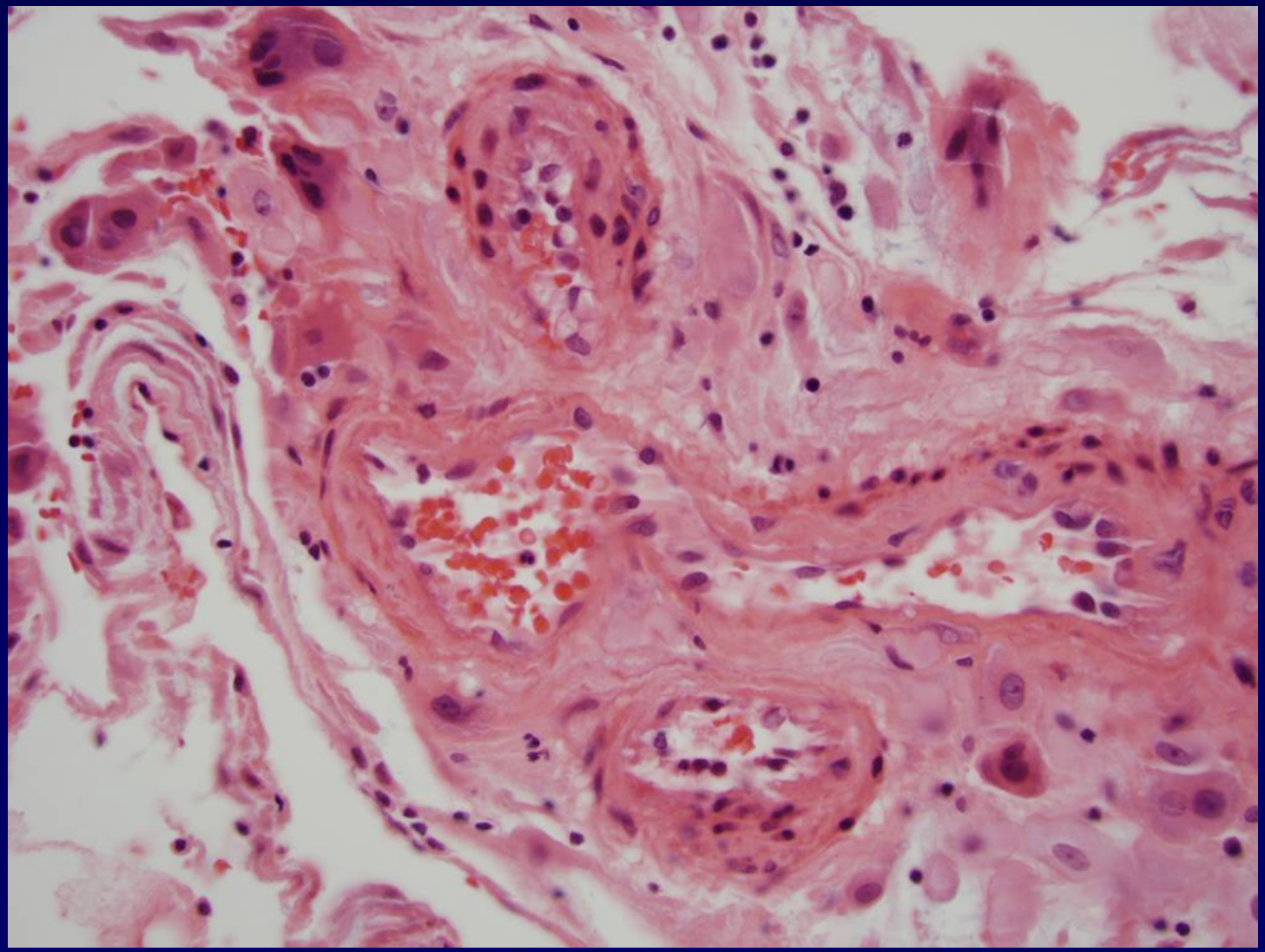
In preeclampsia, second wave of remodeling in intramyometrial segments of spiral arteries doesn't occur

Decidual Vasculopathy



Lack of physiologic transformation

Decidual Vasculopathy



Decidual Vasculopathy

Two forms

- Lack of physiologic transformation
- Acute atherosis
- Both are associated with
  - Preeclampsia
  - IUGR
  - Small for gestational age infants

Low Flow Changes

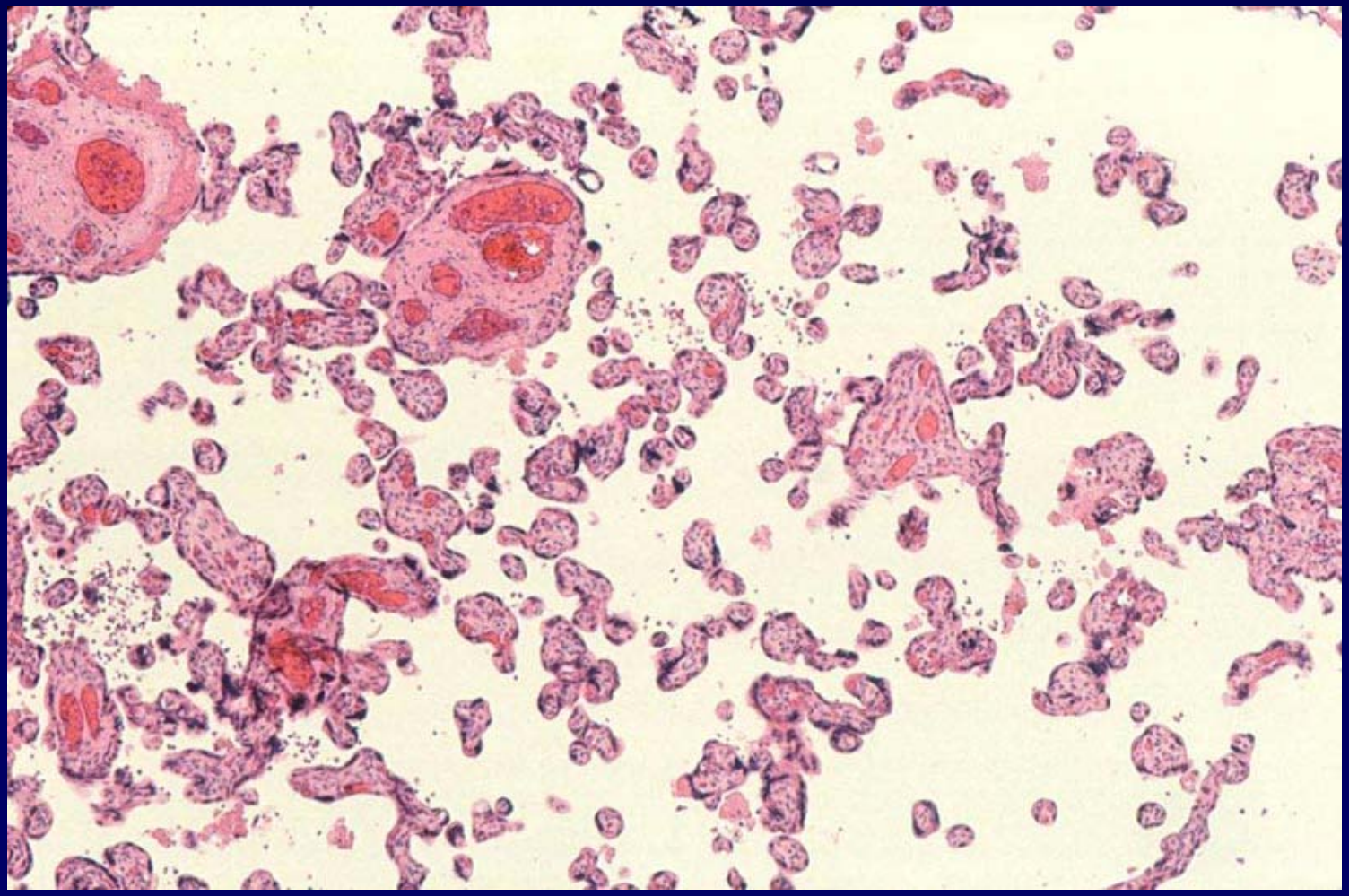
Gross

- small placenta

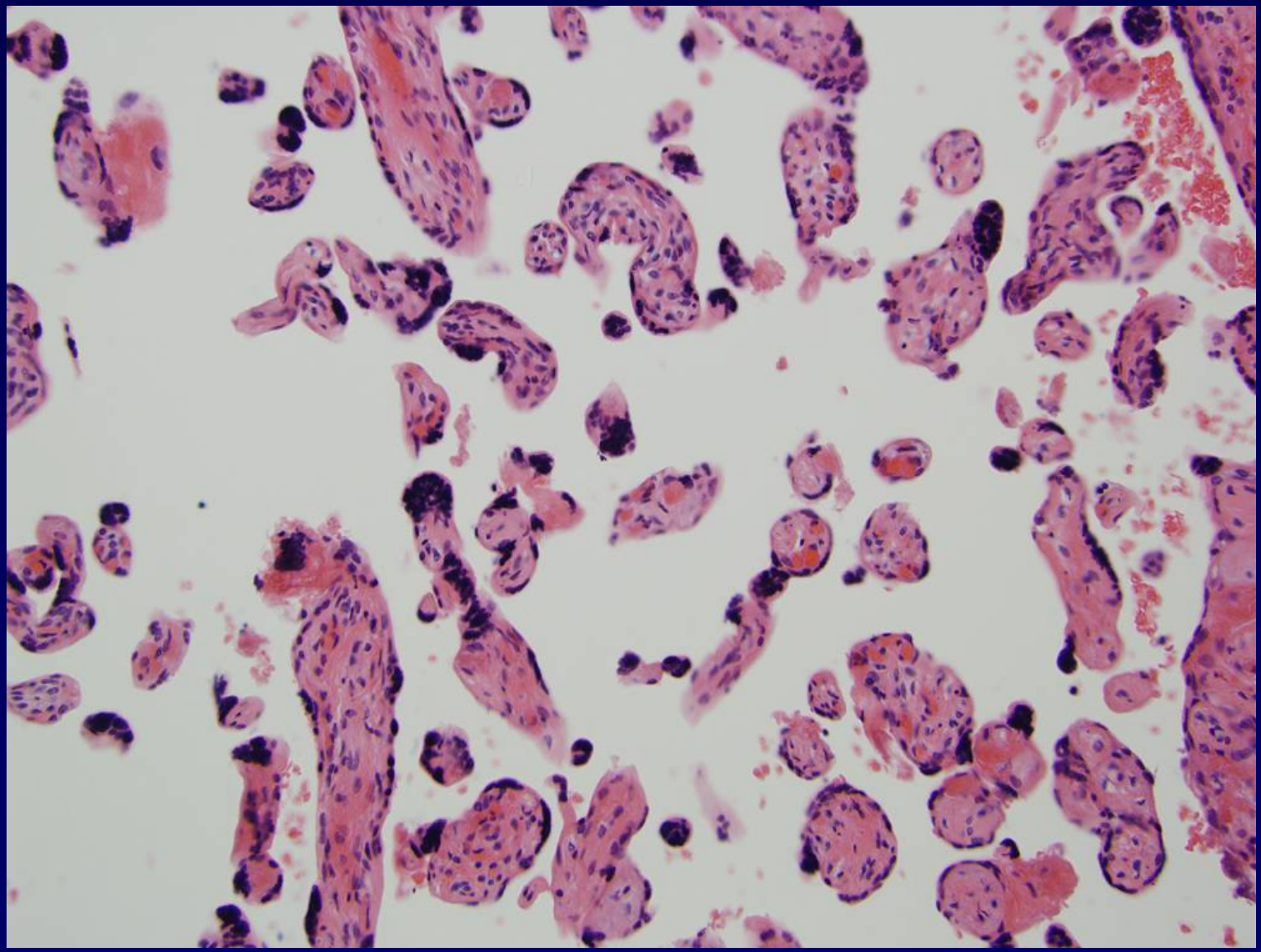
Microscopic

- Very small villi
- Increased syncytial knots
- Prominent villous stroma
- Small fetal capillaries
- Thickened trophoblastic membrane
- Cytotrophoblast proliferation

Low Flow Changes



Low Flow Changes



Preeclampsia

- Most common maternal disease in pregnancy
  - Complicates 2% to 7% of all pregnancies
  - A leading cause of perinatal and maternal morbidity and mortality
- Definition
  - HTN with proteinuria and/or generalized edema after 20 weeks gestation
  - Eclampsia is preeclampsia with seizures

Preeclampsia

Placental findings – characteristic but not specific

- Small placenta
- Decidual vasculopathy
- Low flow changes
- Infarcts
- Retroplacental hematomas
- Intervillous thrombohematomas
- Fetal vascular obstruction

Preeclampsia

Pregnancy-specific

- Delivery is effective treatment

Two stage theory

- Stage 1: reduced placental perfusion
  - Insufficient maternal vascular remodeling
  - Oxidative stress
  - Release of factors that cause clinical sxs
- Stage 2: abnormal maternal vascular response

Preeclampsia

Final common pathway

Diffuse endothelial dysfunction

- Edema
- Platelet consumption
- Renal effects – hypertension, proteinuria
- CNS effects – hyperreflexia, seizures
- Hepatic effects - ↑ LFTs, abdominal pain

Preeclampsia

New insights in pathogenesis

- Hypoxic trophoblast secretes fms-like tyrosine kinase 1 (s-flts-1)
- S-flts-1 binds to VEGF and PlGF → anti-angiogenic effect
- Adenovirus encoding s-flts-1 in rats causes preeclampsia
- Injection of VEGF reverses preeclampsia in rats
  - ? Theraputic role

Preeclampsia

Retrospective data on humans with preeclampsia:

- Increased serum s-flts-1
- Decreased active VEGF and PlGF
- Detected weeks before symptoms
- ? Role as diagnostic test

HELLP Syndrome

hemolysis, ***e***levated ***l***iver enzyme levels, ***l***ow ***p***latelet count

- Complicates 4% to 12% of cases with preeclampsia
- Most occur late 2nd or early 3rd trimester
  - One-third occur post partum
- Placental findings same as preeclampsia

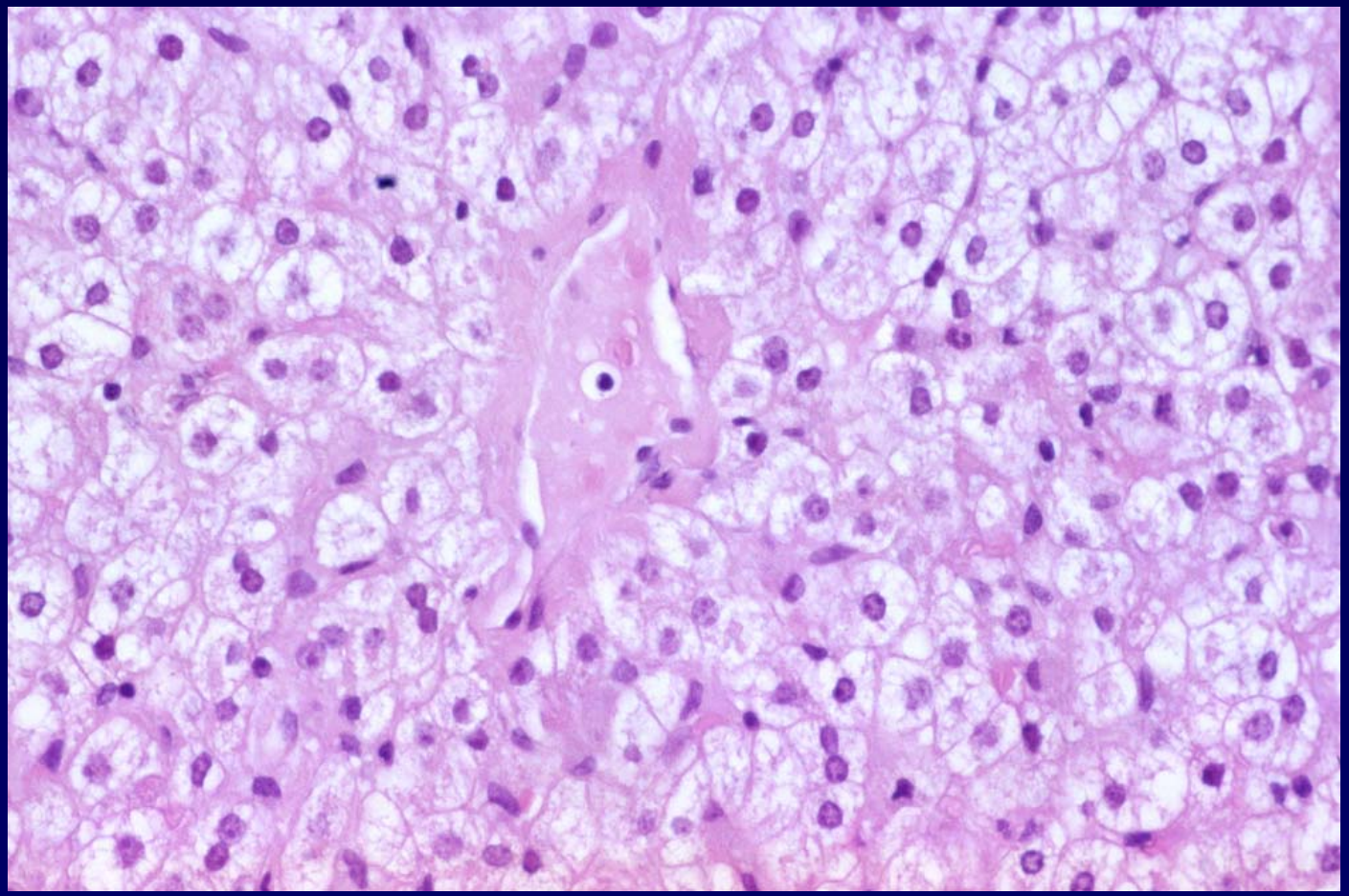
HELLP Syndrome

- Perinatal mortality rate is 35%
- Maternal mortality rate is 1% to 3%
- Abruption correlates with
  - Fetal death
  - Maternal renal failure, pulmonary edema

Acute Fatty Liver of Pregnancy

- Less common than HELLP syndrome
- Higher fetal and maternal mortality
- Clinical presentation
  - Late 3rd trimester
  - Nausea, vomiting, RUQ pain
- Microvesicular steatosis
- Treatment – emergent delivery

Acute Fatty Liver of Pregnancy



Microvesicular steatosis most pronounced in zone 3

Acute Fatty Liver of Pregnancy and HELLP

Pathogenesis

- Fetal enzyme deficiency in beta-oxidation of long chain fatty acids
- Most common is mutation in 3 hydroxyacyl-coenzyme A dehydrogenase gene
- Deficiency causes infant-childhood
  - Hepatic encephalopathy
  - Cardiomyopathy
  - Peripheral neuropathy
  - Skeletal myopathy

Acute Fatty Liver of Pregnancy and HELLP

- Placenta shares fetal genotype
- Placental enzyme deficiency causes accumulation of toxic intermediates
- How intermediates cause maternal disease is unclear
- Two-thirds deliver prematurely
- 40% are growth restricted

Essential Hypertension

- Little information about placental findings in isolated essential hypertension
- Hyperplastic arteriosclerosis
  - Proliferation of all vessel wall layers
  - Intimal hyperplasia
  - Luminal narrowing
  - Most pronounced in myometrial segments

Systemic Lupus Erythematosus

SLE associated with significantly increased

- Stillbirth
- IUGR
- Prematurity

Systemic Lupus Erythematosus

SLE alone

- Decreased placental weight
- Low flow changes
- Decidual vasculopathy
- Decidual thrombi
- Fetal vascular obstruction
- Villitis of unknown etiology

May occur in 1st trimester

Do not correlate with disease severity

Systemic Lupus Erythematosus

30% to 40% have antiphospholipid antibodies

- Autoantibodies against phospholipids
- Arterial and venous thromboembolic events
- Thrombocytopenia
- Fetal loss

Systemic Lupus Erythematosus

SLE and antiphospholipid antibodies

- Significant increase in
  - Low flow changes
  - Extensive infarction
  - Fetal death

Antiphospholipid Antibodies

If + anticardiolipin and + lupus anticoagulant:

High rate of

- Decidual vasculopathy
- Decidual thrombosis
- Extensive infarction
- Fetal loss

Ogishima D et al. Pathol Int 2000; 5-:224-229

Maternal Thrombophilic Conditions

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V mutation (Leiden)
- Prothrombin 20120A
- MTHFR C677T- hyperhomocysteinemia

Maternal Thrombophilic Conditions

Clinical associations

- Controversial
- Preeclampsia
- Late pregnancy loss
- Intrauterine growth restriction

Hereditary Thrombophilic Conditions

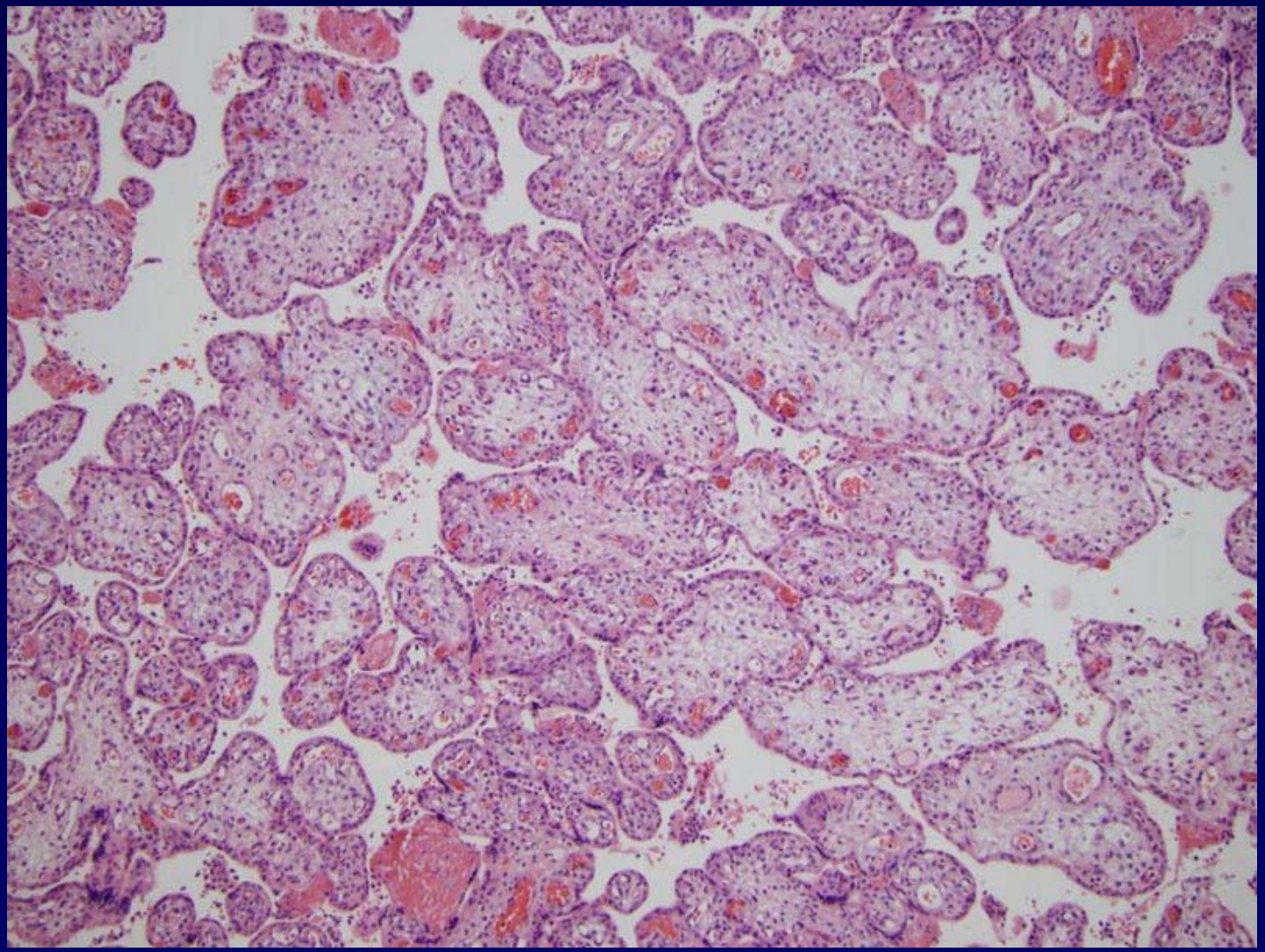
- Problems
  - Poor study design
  - Imprecise placental terminology
- May be associated with
  - ↑ number, ↑ size of infarcts
  - Acute atherosis, spiral artery thrombi
  - Retroplacental hematoma/abruption
  - Fetal vascular obstruction

Diabetes

Placental findings are variable, non-specific

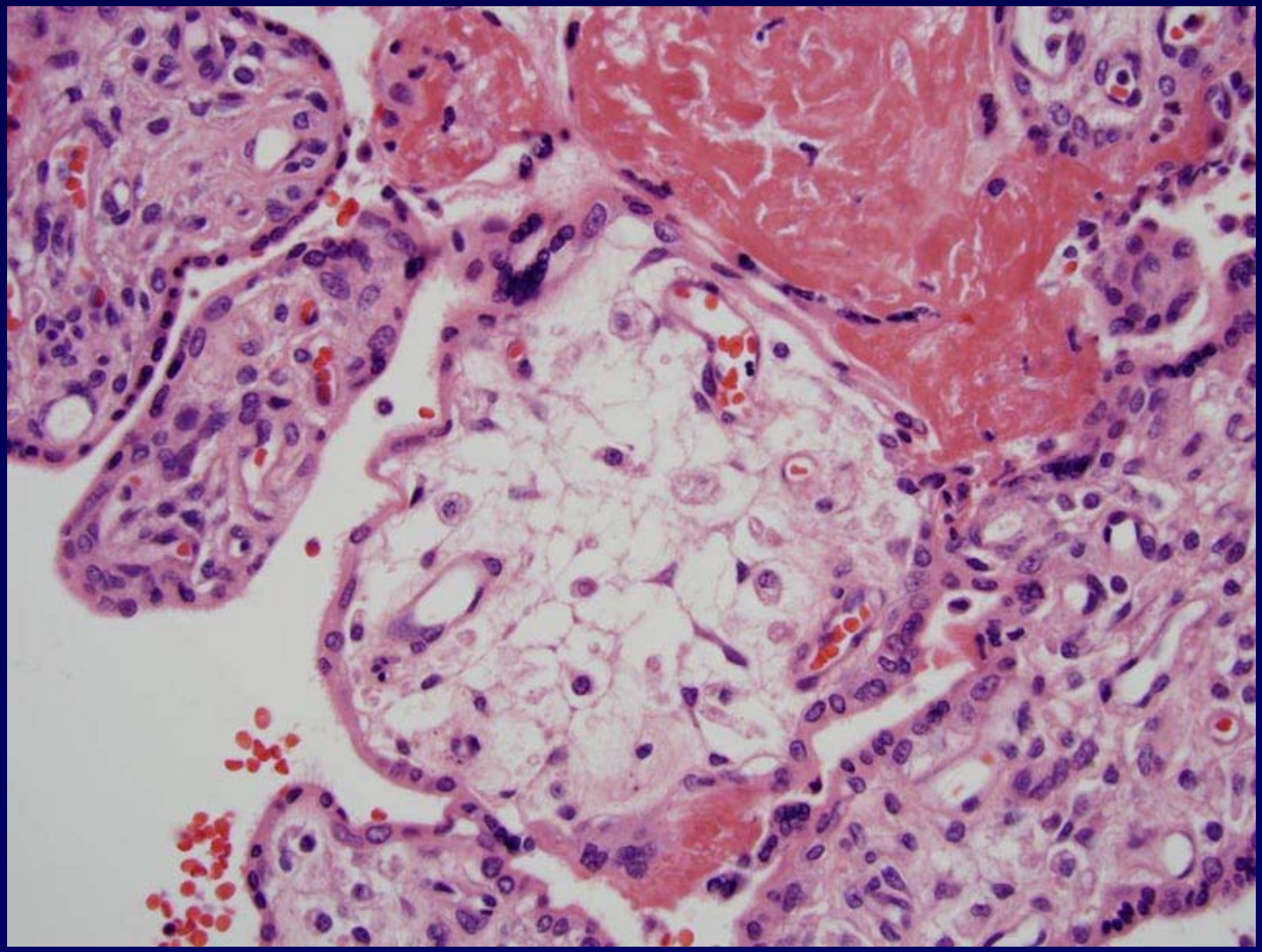
- Gross findings
  - Sometimes normal
  - Over 50% are larger, heavier than normal
- Microscopic findings
  - Immature, edematous villi
  - Prominent cytotrophoblast
  - Irregularly thickened trophoblastic membranes
  - Fibrinoid deposits

Diabetes



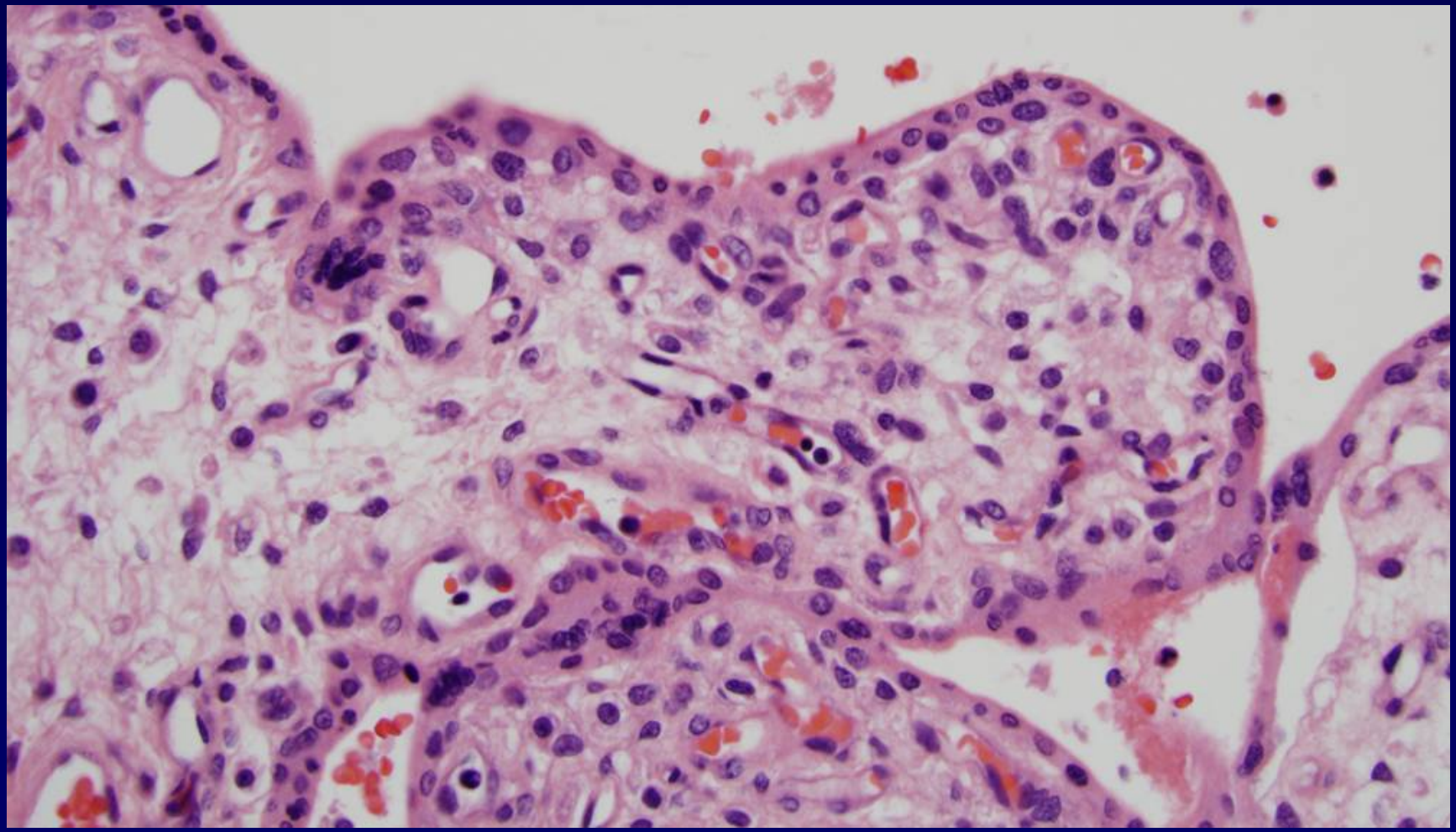
Enlarged, immature villi

Diabetes



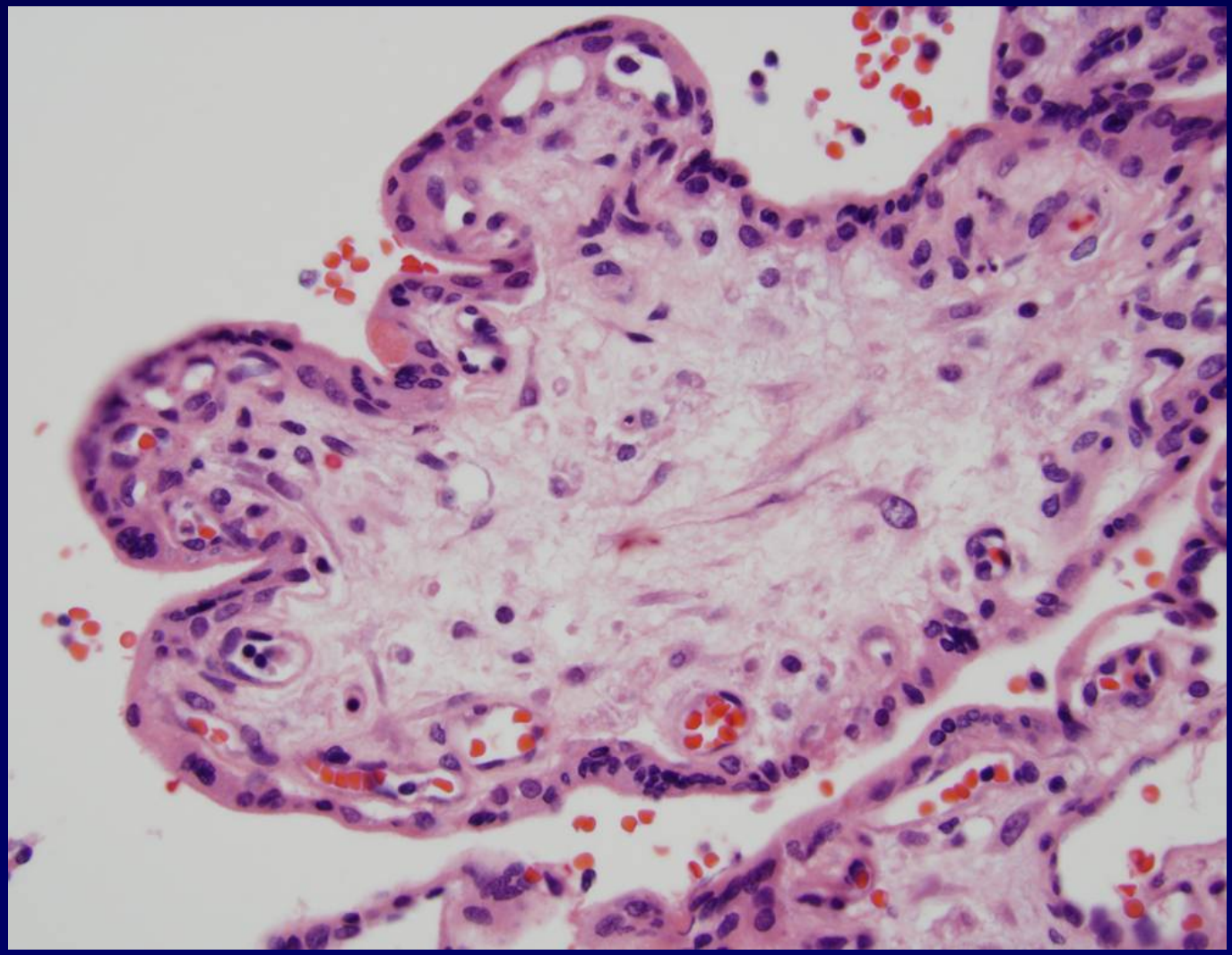
Villous edema

Diabetes



Prominent cytotrophoblast

Diabetes



Thickened basement membrane

Diabetes

Associated placental findings

- Chorangiosis
- Uniformly avascular terminal villi
- Single umbilical artery
- Increased cord diameter

Diabetes

Placental changes do not correlate with:

- Size of infant
- Degree of glycemic control

Diabetes

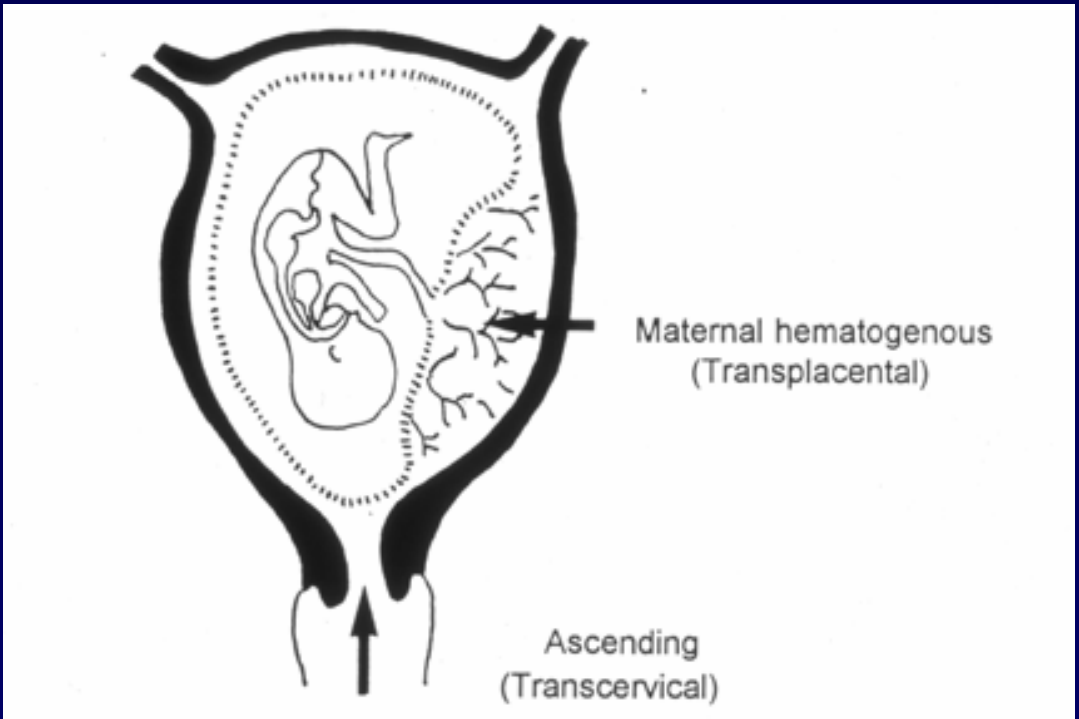
Fetal complications

- More common if type 1
- Congenital malformations
- Macrosomia
- “unexplained” fetal death
- Not related to presence or severity of placental findings

Intrauterine Infection Complications

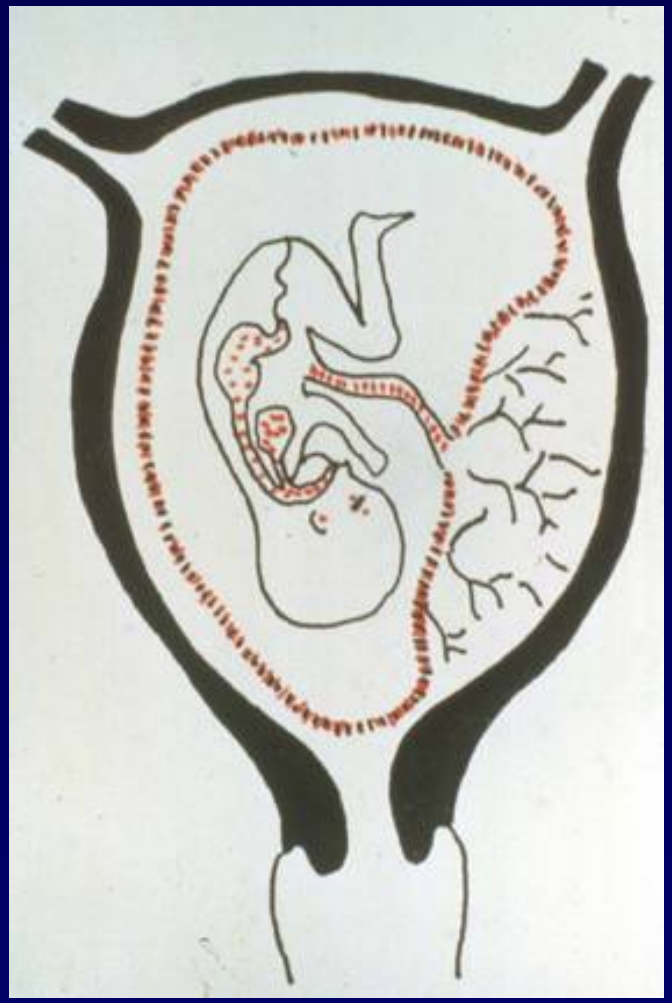
- Abortion
- Stillbirth
- Malformation
- Acute infection
- Delayed sequelae

Pathogenesis of Intrauterine Infection



- Ascending - typically bacterial → chorioamnionitis
- Transplacental - viral, protozoal → villitis

Ascending Infection



- Most common type of infection
- Organisms enter through cervix
- Relationship with rupture of membranes
- Inflammation of fetal membranes and umbilical cord
- Neonatal pneumonia, sepsis by swallowing, aspirating infected amnionic fluid

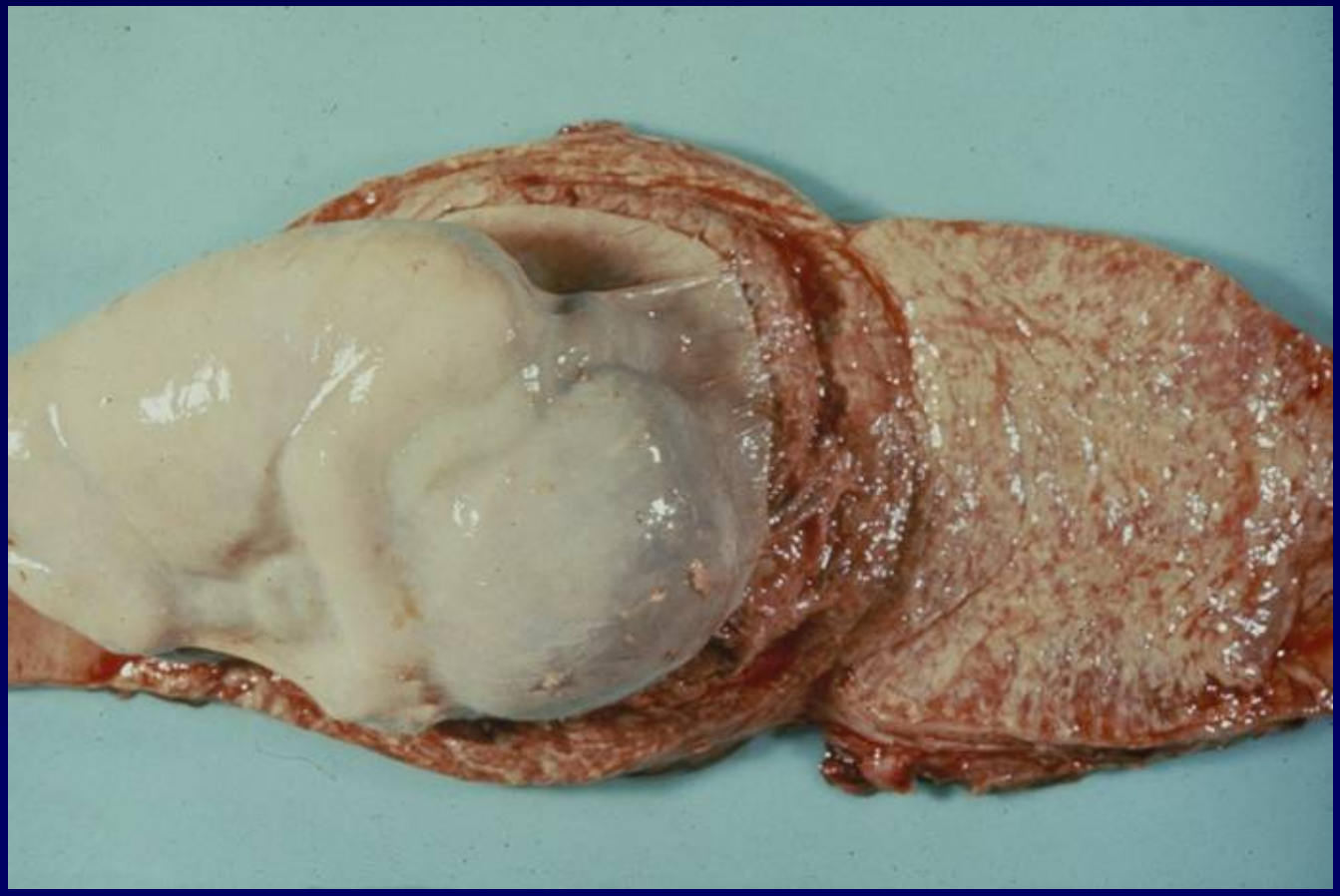
Chorioamnionitis – Incidence

• Fox and Langley	24%	1,000 consecutive
• Salafia	4%	normal term
• Hillier	67%	preterm
	21%	term
• Russell	55%	21-28 weeks
	11%	33-36 weeks
	4%	37-40 weeks

Chorioamnionitis – Organisms

- E. coli
- Staphylococci
- Streptococci
- Proteus mirabilis
- Klebsiella
- Ureaplasma
- Bacteroides fragilis
- Fusobacterium sp.
- Listeria monocytogenes
- Myoplasma
- Candida albicans

Acute Chorioamnionitis



Thick, opaque, granular

May be foul-smelling

Ascending Infection

- Maternal response – acute chorioamnionitis
  - In free membranes polys emigrate from decidual vessels through chorion and amnion
  - In placenta polys emigrate from intervillous space through chorion and amnion
- Fetal response – funisitis, chorionic vasculitis
  - Polys emigrate from umbilical vessels
  - Polys emigrate from chorionic vessels

Ascending Infection

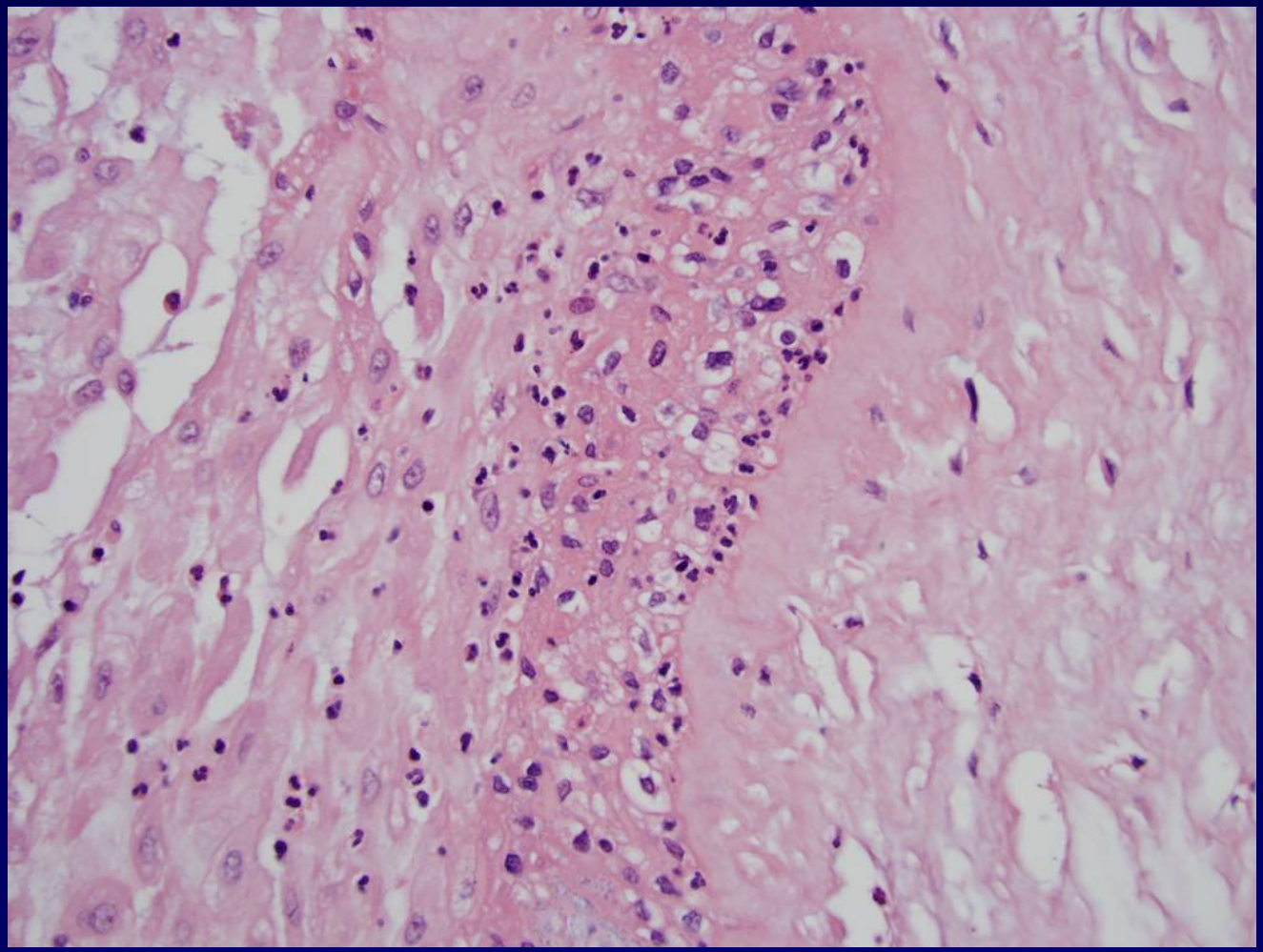
- Because of evidence that inflammation relates to outcomes, better standardization of diagnostic terminology is needed
- Redline RW et al. (Pediatr Dev Pathol 6:435-448, 2003) have proposed a scheme for staging and grading the maternal and fetal response

Maternal Inflammatory Response Stage 1

- Suggested diagnostic terminology
  - Acute subchorionitis or acute chorionitis
- Definition
  - Polys in subchorionic fibrin and/or membrane trophoblast

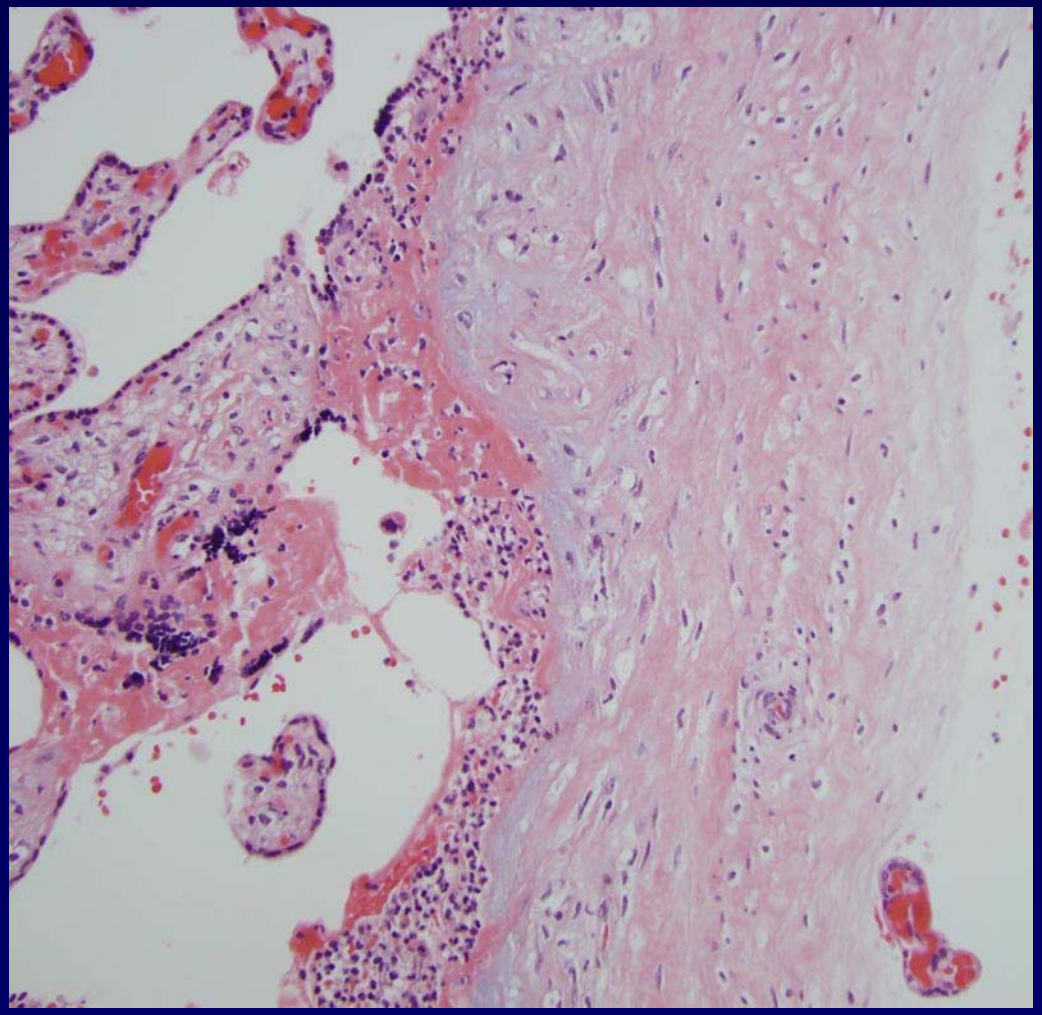
Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Maternal Inflammatory Response
Stage 1- Acute Chorionitis



Polys in membrane trophoblast

Maternal Inflammatory Response
Stage 1- Acute Chorionitis



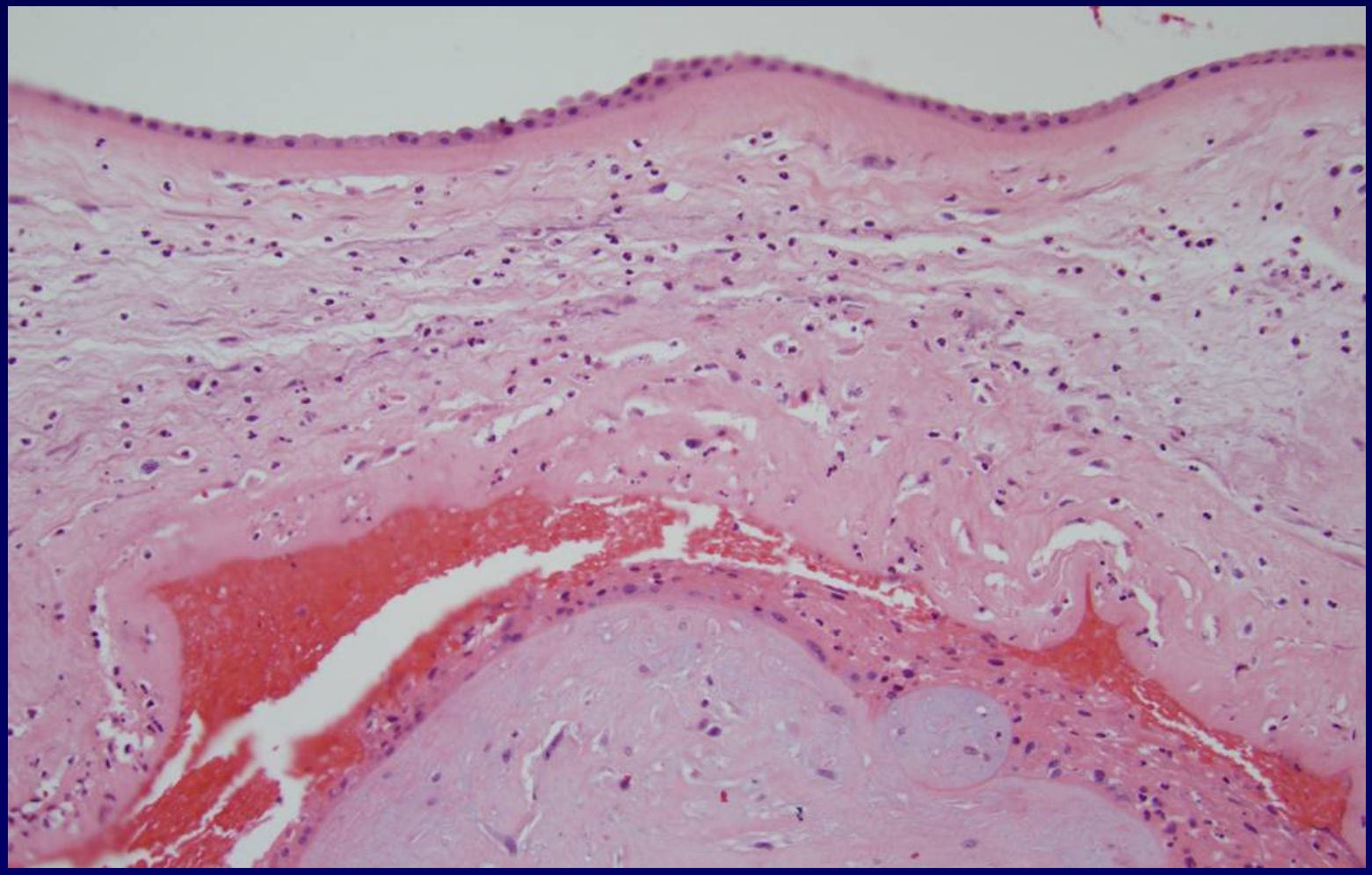
Polys in fibrin beneath chorionic plate

Maternal Inflammatory Response Stage 2

- Suggested diagnostic terminology
  - Acute chorioamnionitis
- Definition
  - Diffuse-patchy polys in fibrous chorion and/or amnion

Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Maternal Inflammatory Response
Stage 2 – Acute Chorioamnionitis



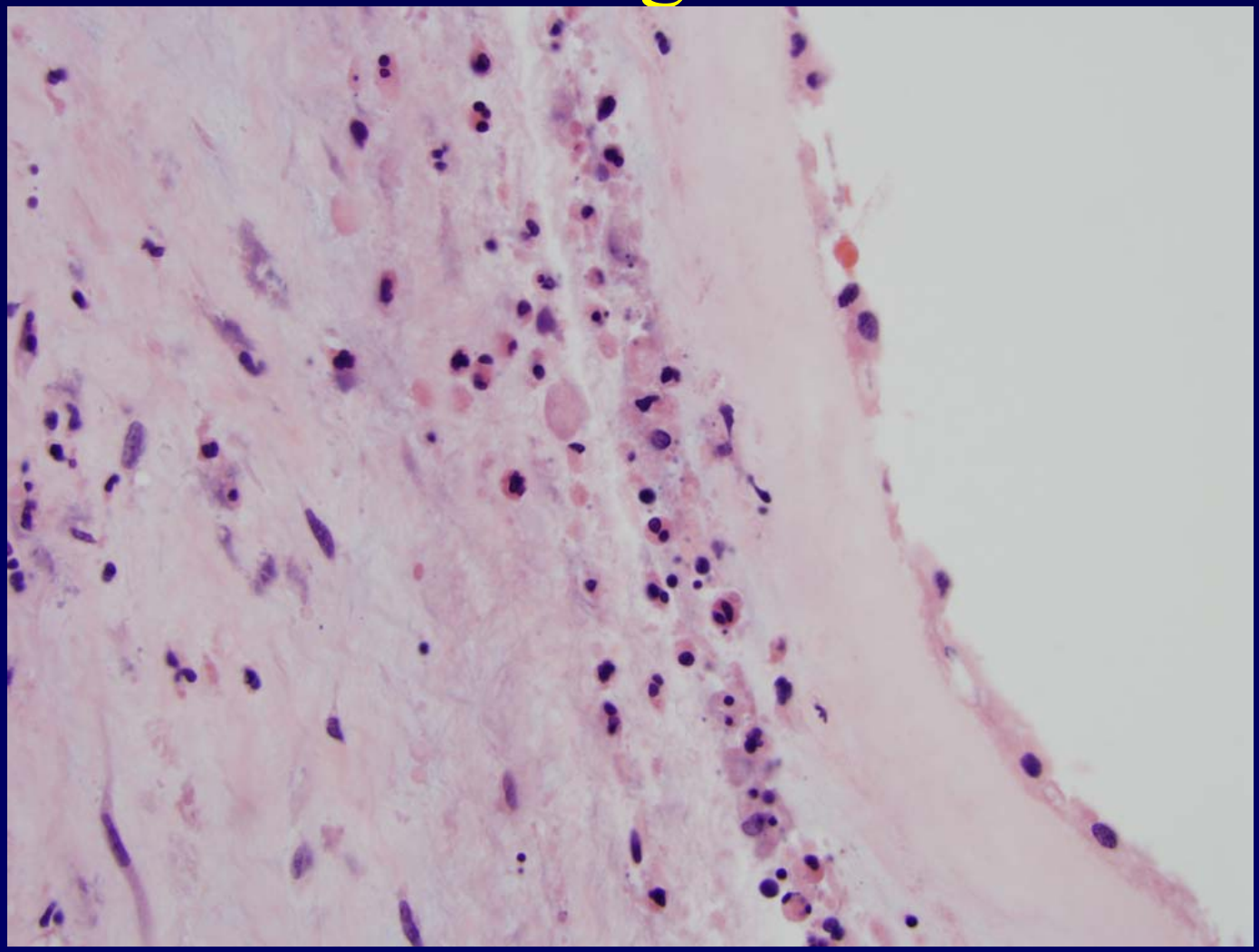
Polys in chorion and amnion

Maternal Inflammatory Response Stage 3

- Suggested diagnostic terminology
  - Necrotizing chorioamnionitis
- Definition
  - Poly karyorrhexis, amnion necrosis and/or amniotic basement membrane thickening/hypereosinophilia

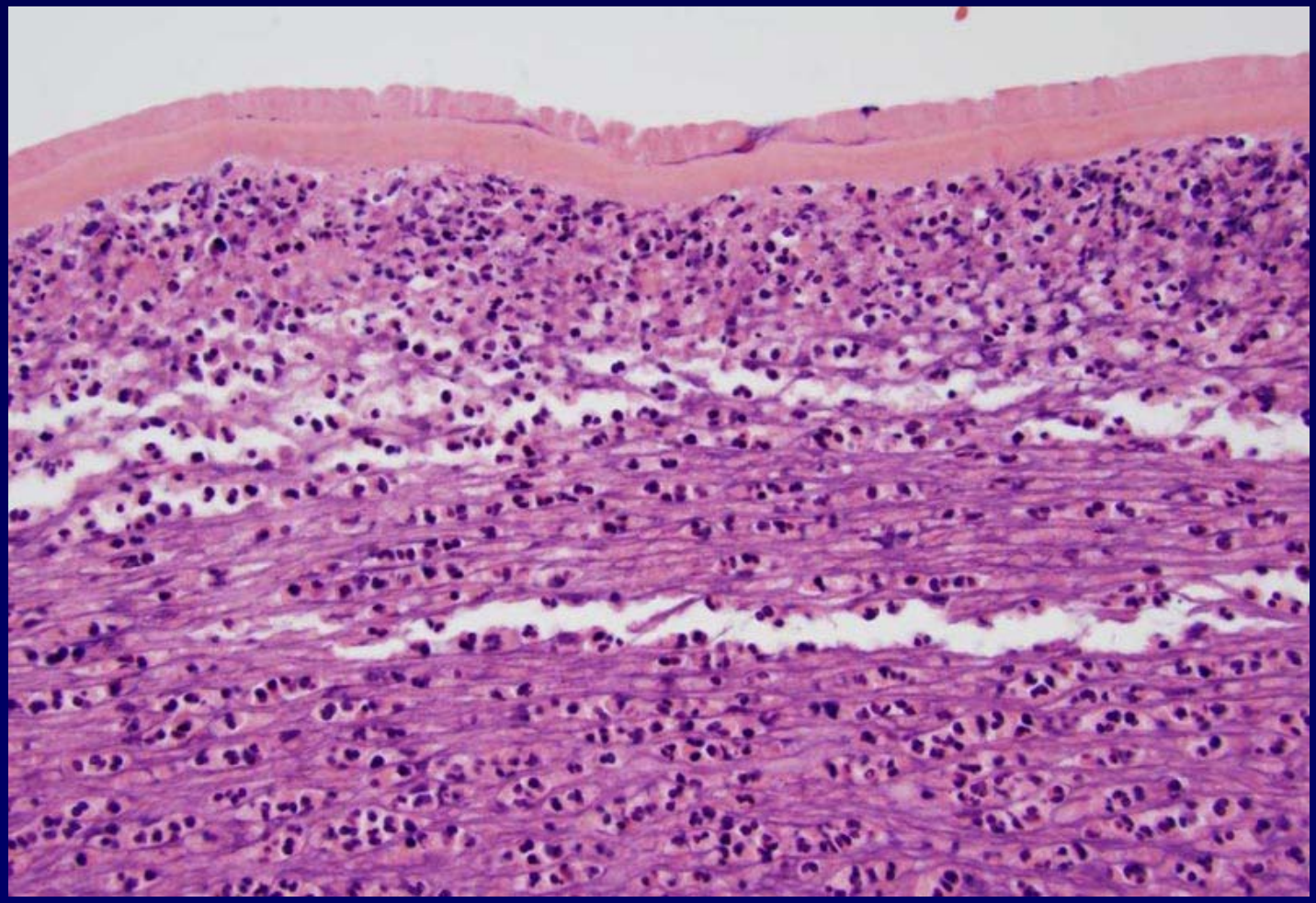
Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Maternal Inflammatory Response
Stage 3



Polys with karyorrhexis

Maternal Inflammatory Response Stage 3 – Necrotizing Chorioamnionitis



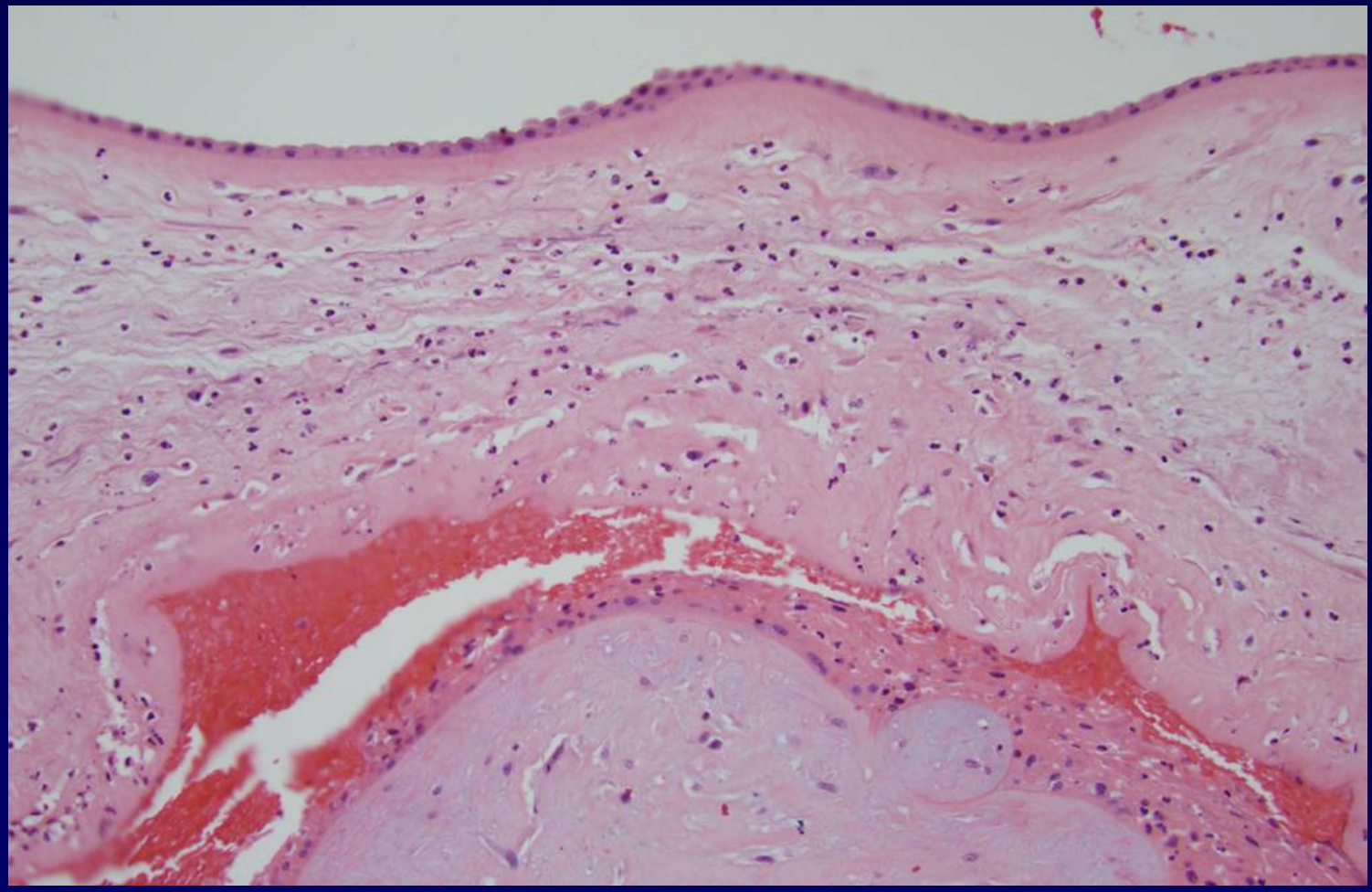
Amniotic epithelial necrosis, thickened basement membrane

Maternal Inflammatory Response Grade 1 – Mild-Moderate

- Suggested diagnostic terminology
  - Mild or moderate
- Definition
  - Not severe

Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Maternal Inflammatory Response Grade 1- Mild-Moderate



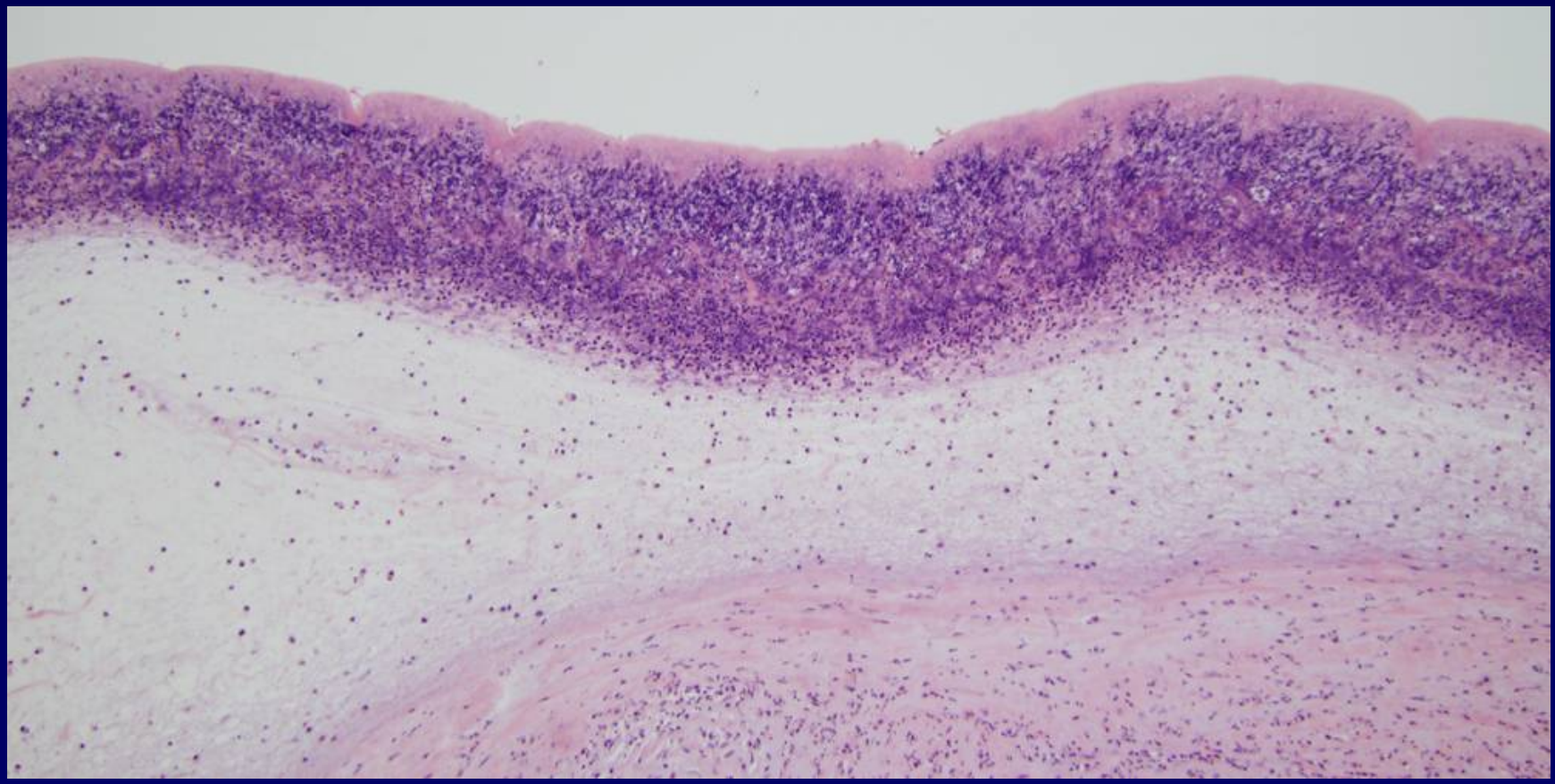
Scattered polys

Maternal Inflammatory Response Grade 2 - Severe

- Suggested diagnostic terminology
  - Severe acute chorioamnionitis *or* with subchorionic microabscesses
- Definition
  - Confluent polys between chorion and decidua; > or equal to 3 isolated foci or continuous band

Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Maternal Inflammatory Response
Grade 2 - Severe



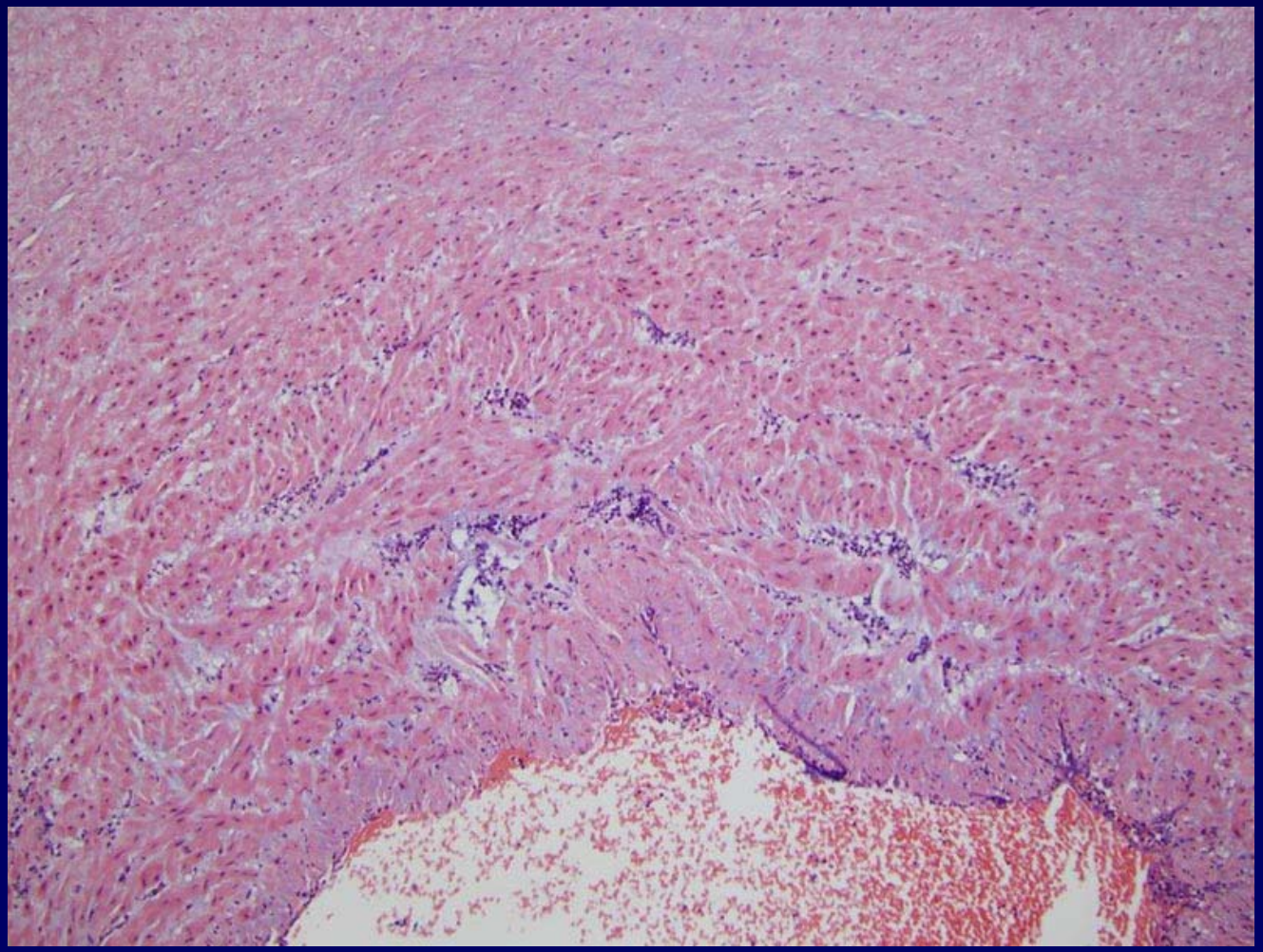
Confluent band of polys

Fetal Inflammatory Response Stage 1

- Suggested diagnostic terminology
  - With chorionic vasculitis *or* umbilical phlebitis
- Definition
  - Intramural polys in chorionic vessels and/or umbilical vein

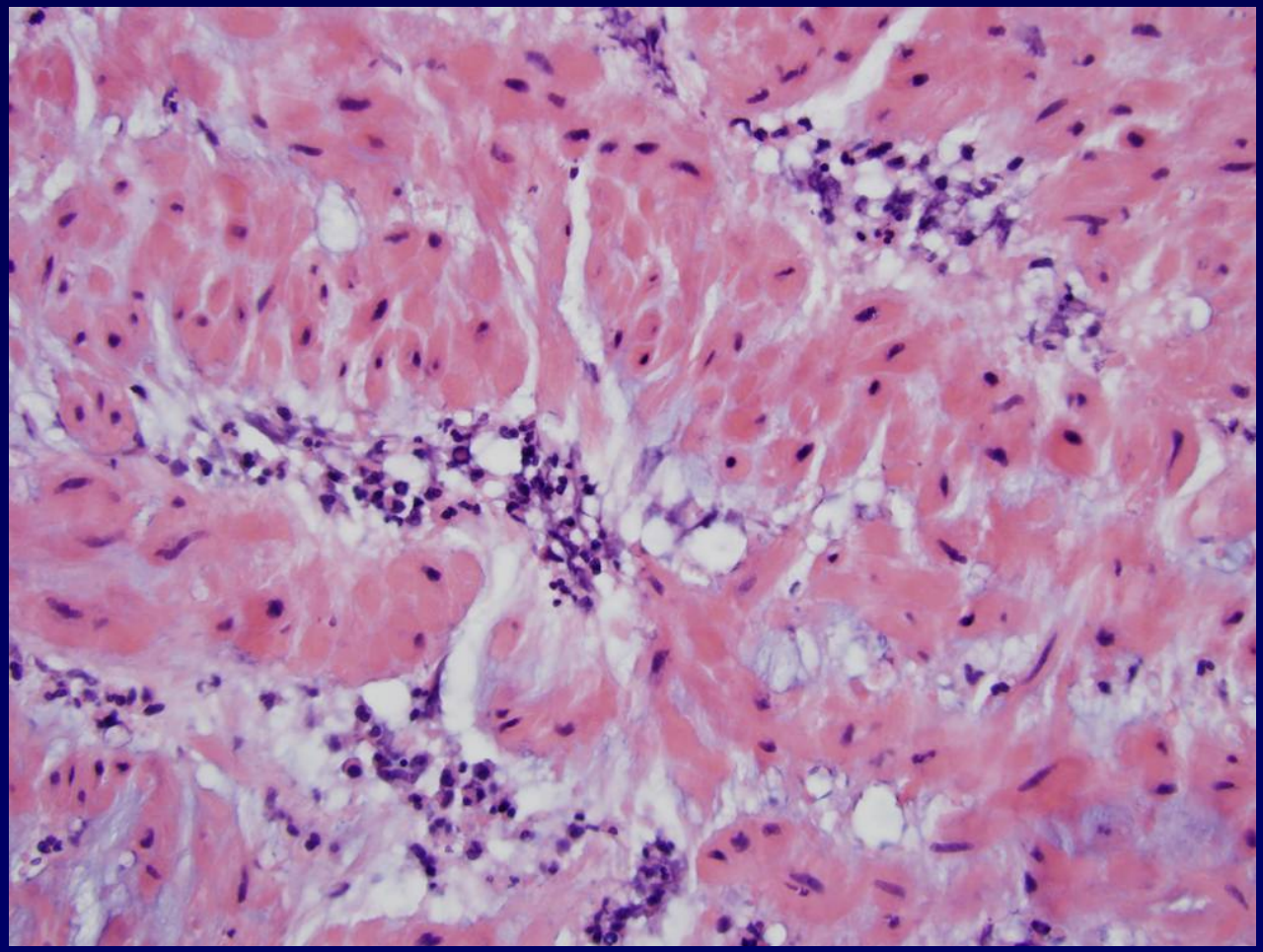
Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Fetal Inflammatory Response
Stage 1 - Phlebitis



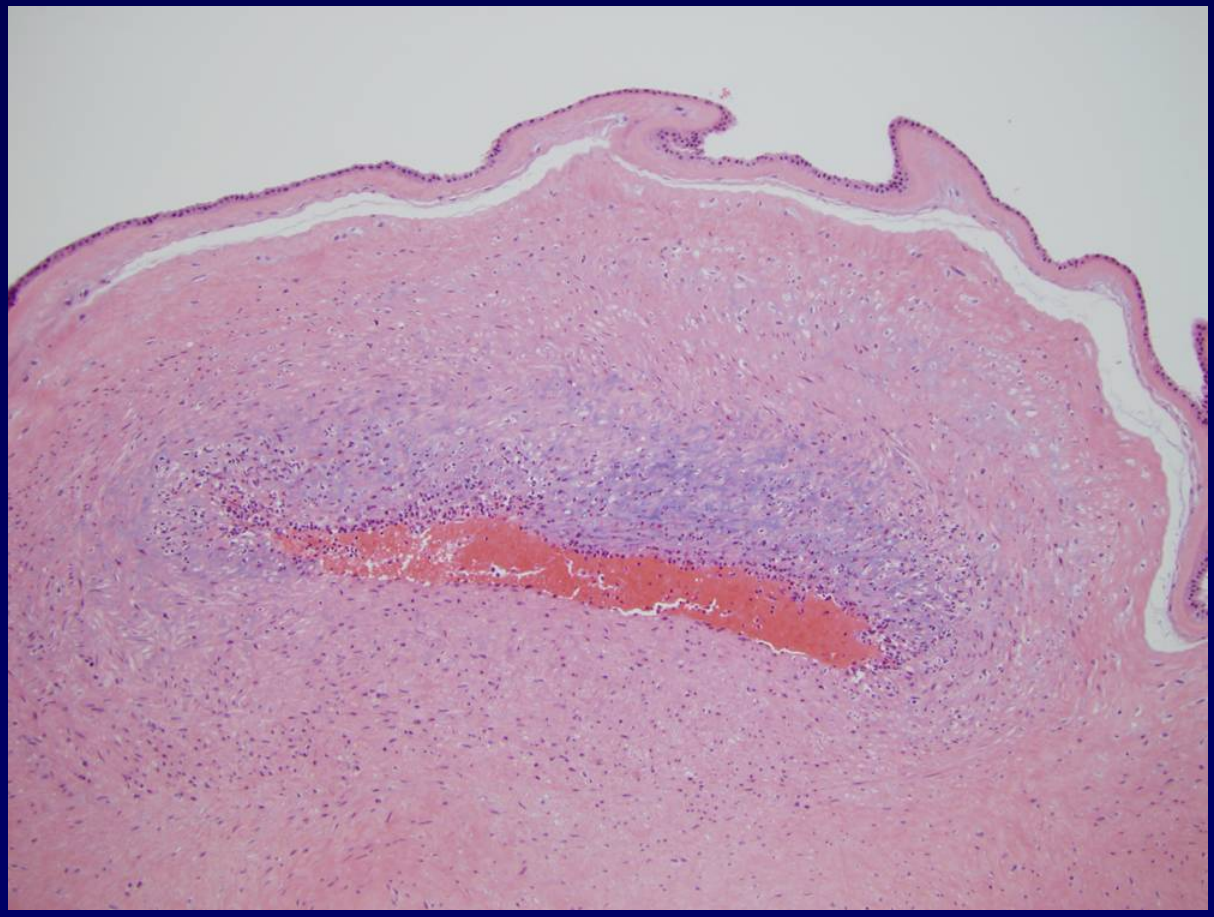
Polys in smooth muscle of umbilical vein wall

Fetal Inflammatory Response
Stage 1 - Phlebitis



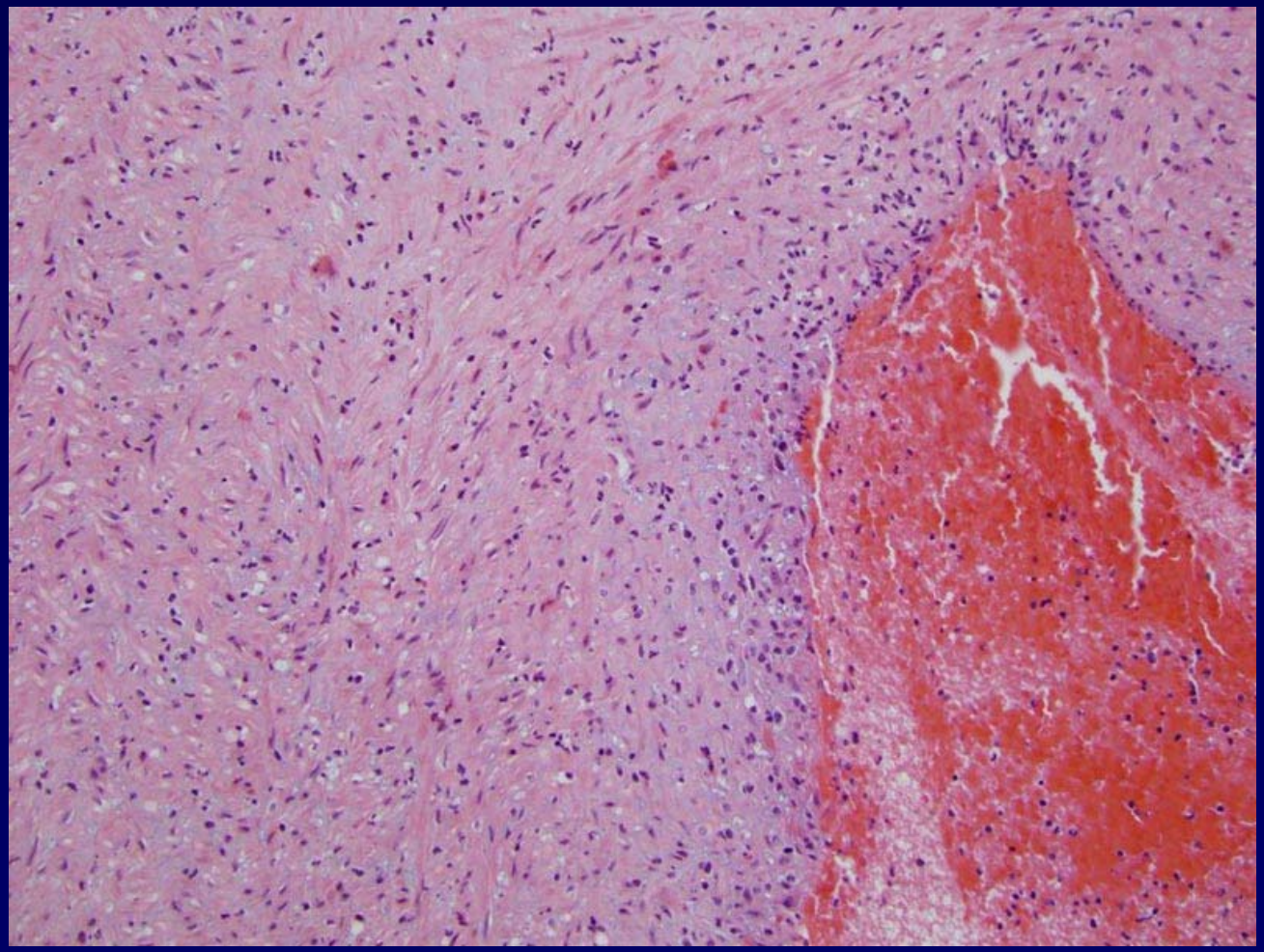
Polys in smooth muscle of umbilical vein wall

Fetal Inflammatory Response
Stage 1 - Chorionic Vasculitis



Polys in wall of large chorionic vessels on fetal plate

Fetal Inflammatory Response
Stage 1 - Chorionic Vasculitis



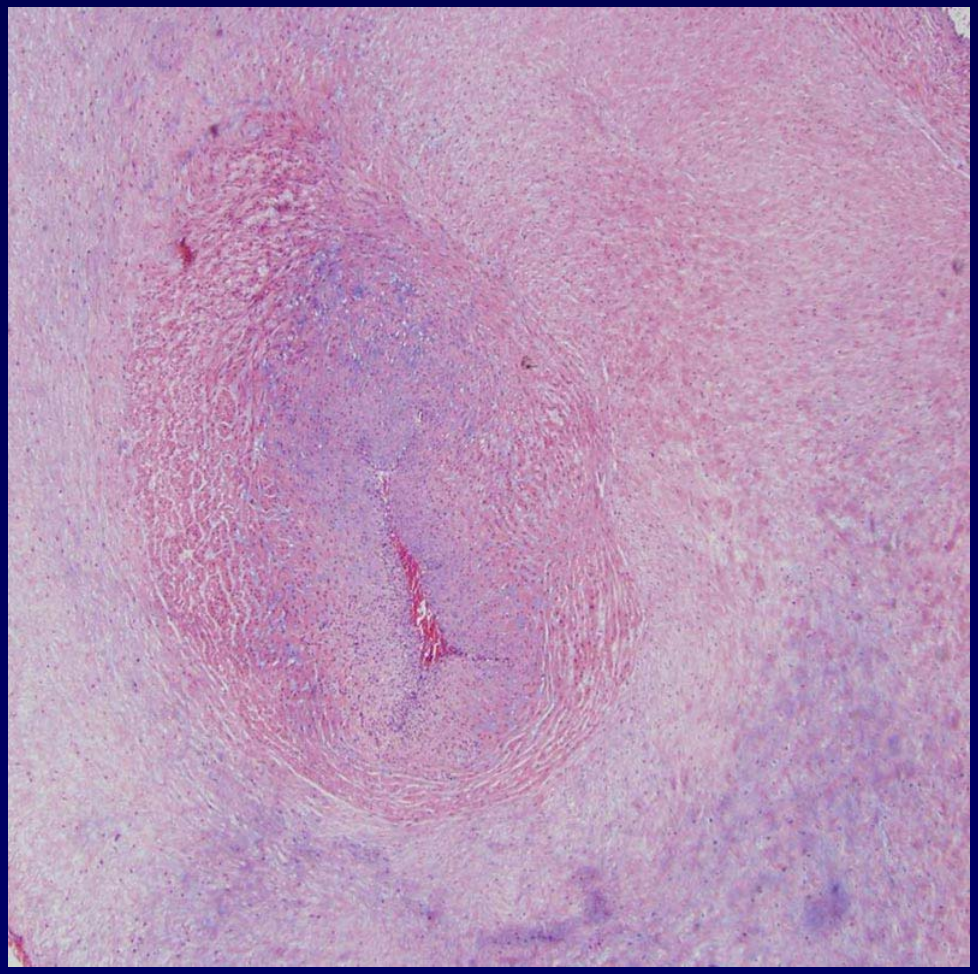
Side of vessel towards amniotic cavity has numerous polys

Fetal Inflammatory Response Stage 2

- Suggested diagnostic terminology
  - With umbilical vasculitis (one or both arteries +/- vein) *or* umbilical panvasculitis (all vessels)
- Definition
  - Intramural polys in umbilical artery or arteries (+/- vein)

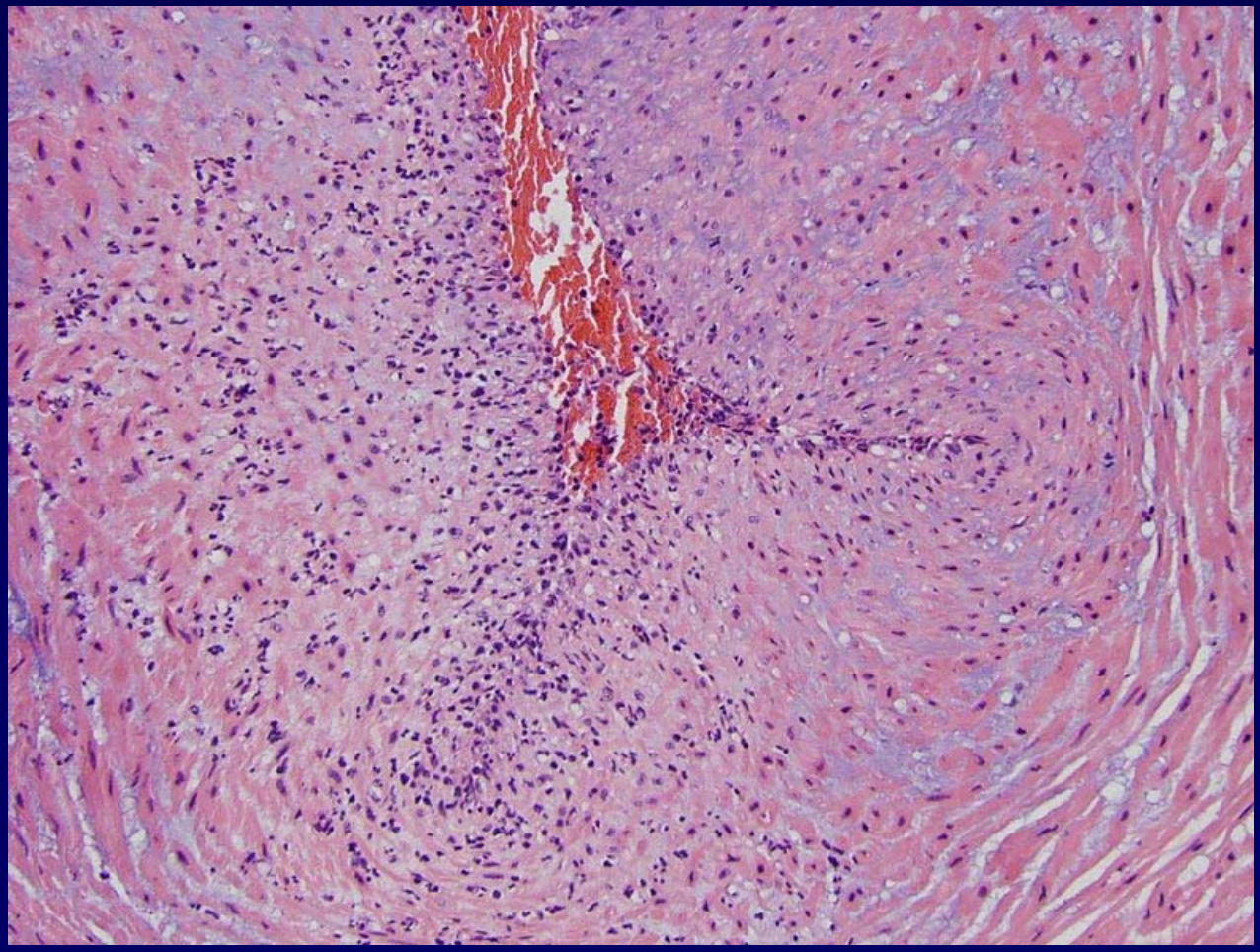
Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Fetal Inflammatory Response
Stage 2 - Arteritis



Polys in smooth muscle of wall of umbilical artery

Fetal Inflammatory Response
Stage 2 - Arteritis



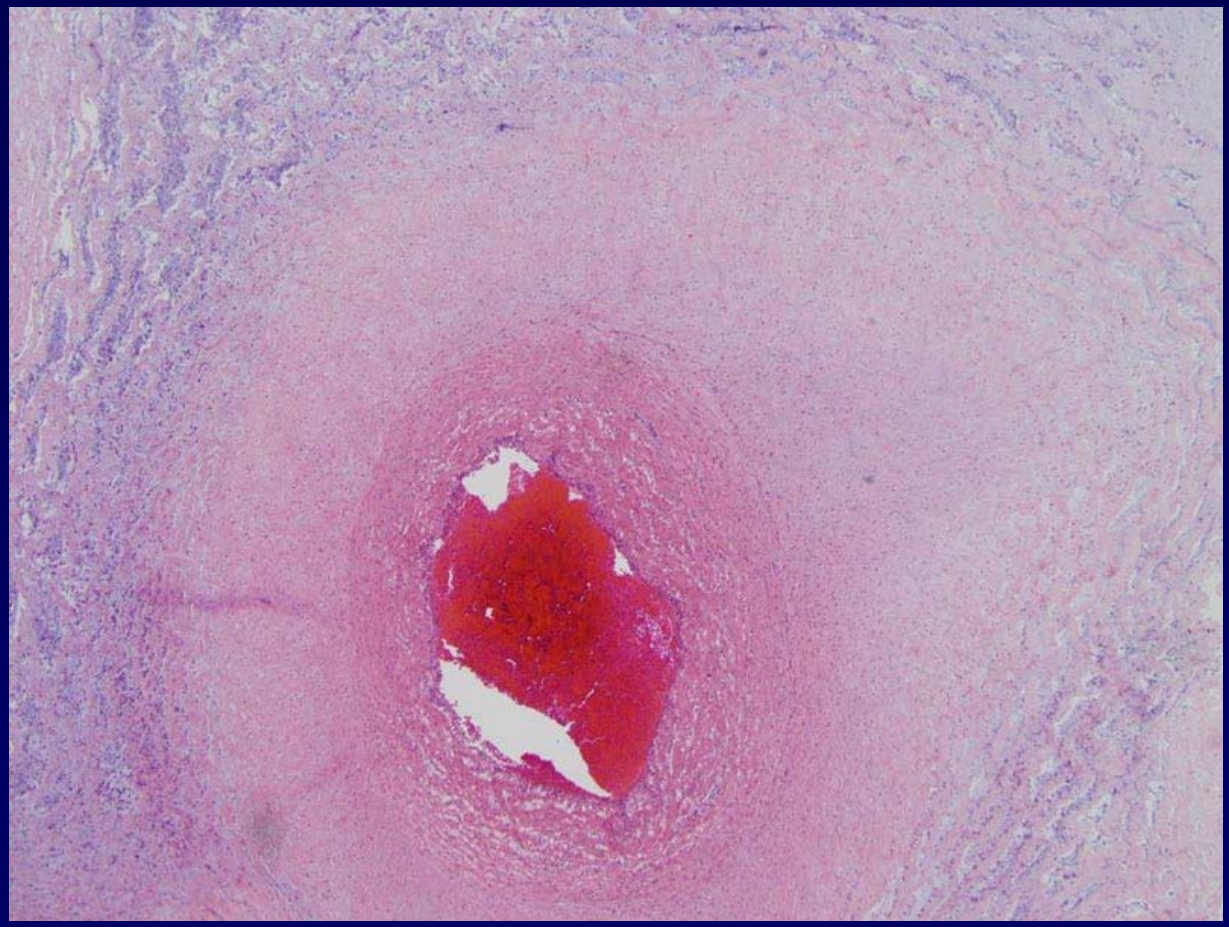
Polys in smooth muscle of wall of umbilical artery

Fetal Inflammatory Response Stage 3

- Suggested diagnostic terminology
  - With necrotizing funisitis *or* with concentric umbilical perivasculitis
- Definition
  - Polys +/- debris in concentric bands-rings-halos around one or more umbilical vessels

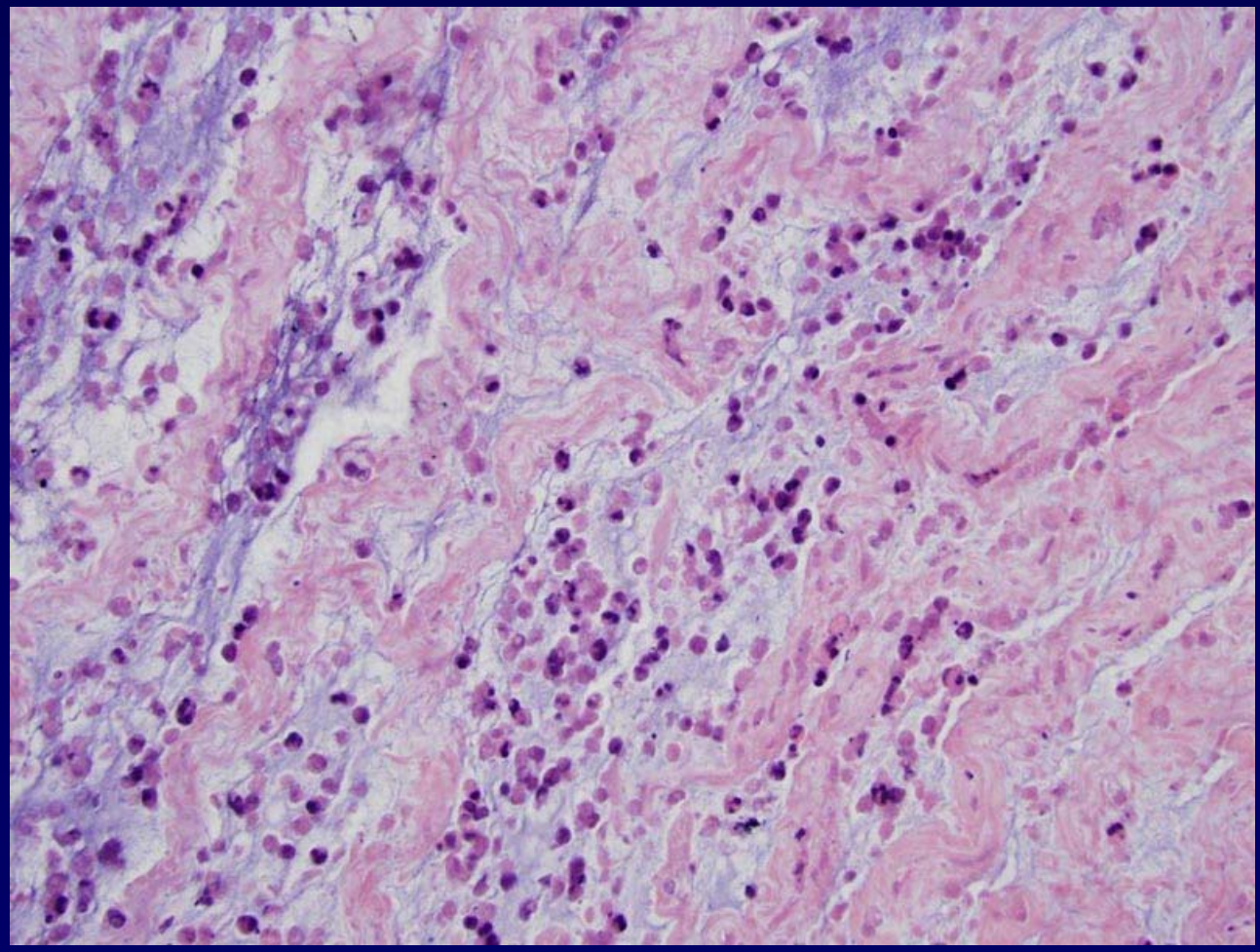
Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

Fetal Inflammatory Response
Stage 3 - Necrotizing Funisitis



Polys and debris ring the umbilical vessels

Fetal Inflammatory Response
Stage 3 - Necrotizing Funisitis



Fetal Inflammatory Response Grade 1 - Mild-Moderate

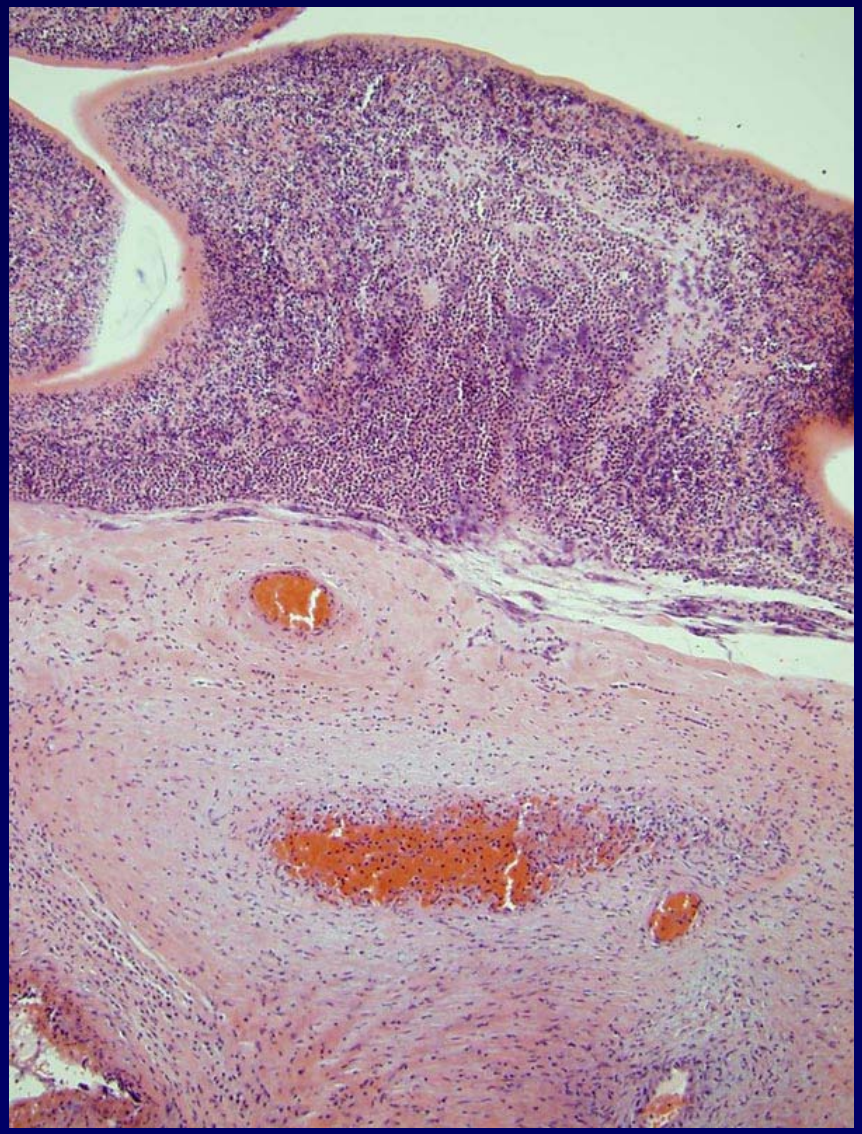
- Suggested diagnostic terminology
  - Mild – moderate
- Definition
  - Not severe

Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

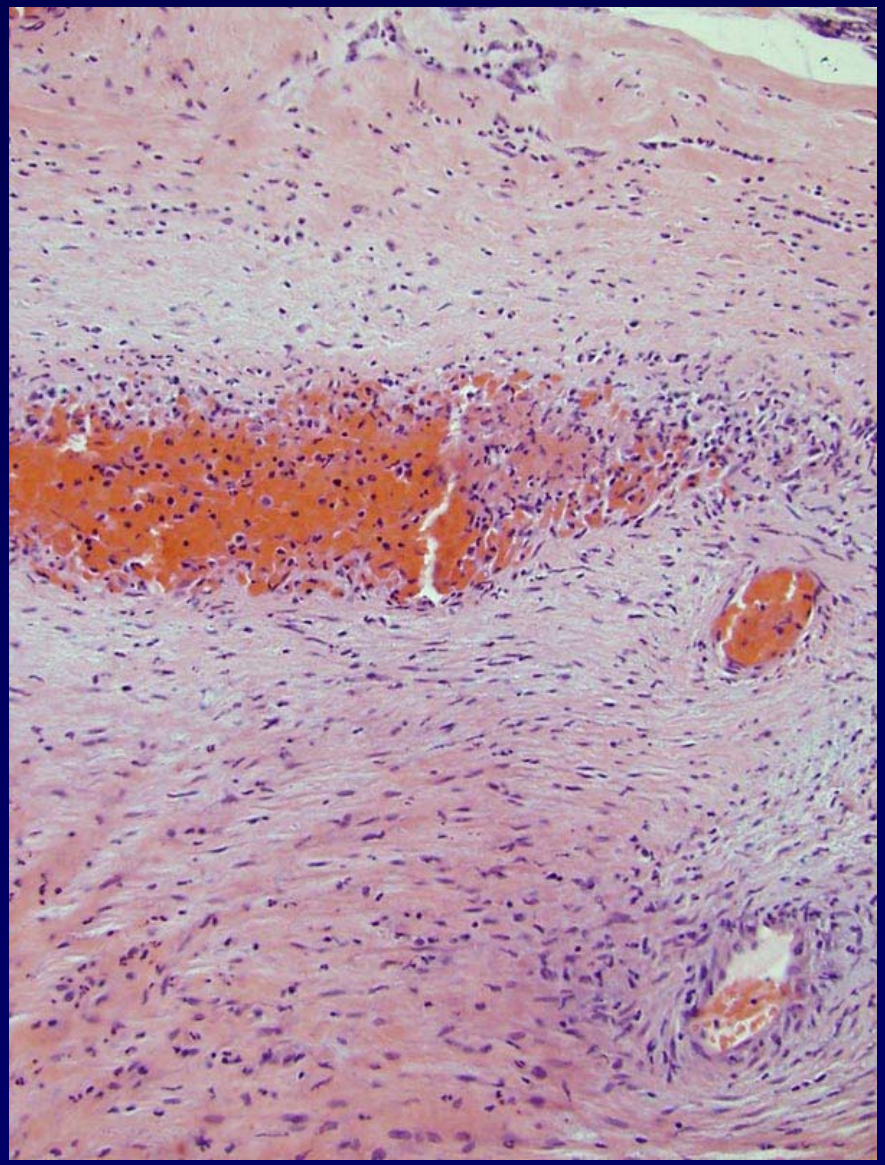
Fetal Inflammatory Response Grade 2 - Severe

- Suggested diagnostic terminology
  - With a severe fetal inflammatory response *or* with intense chorionic (umbilical) vasculitis
- Definition
  - Near confluent intramural polys in chorionic and/or umbilical vessels with attenuation/degeneration of vascular smooth muscle
  - Redline RW et al. Pediatr Dev Pathol 6:435-448, 2003

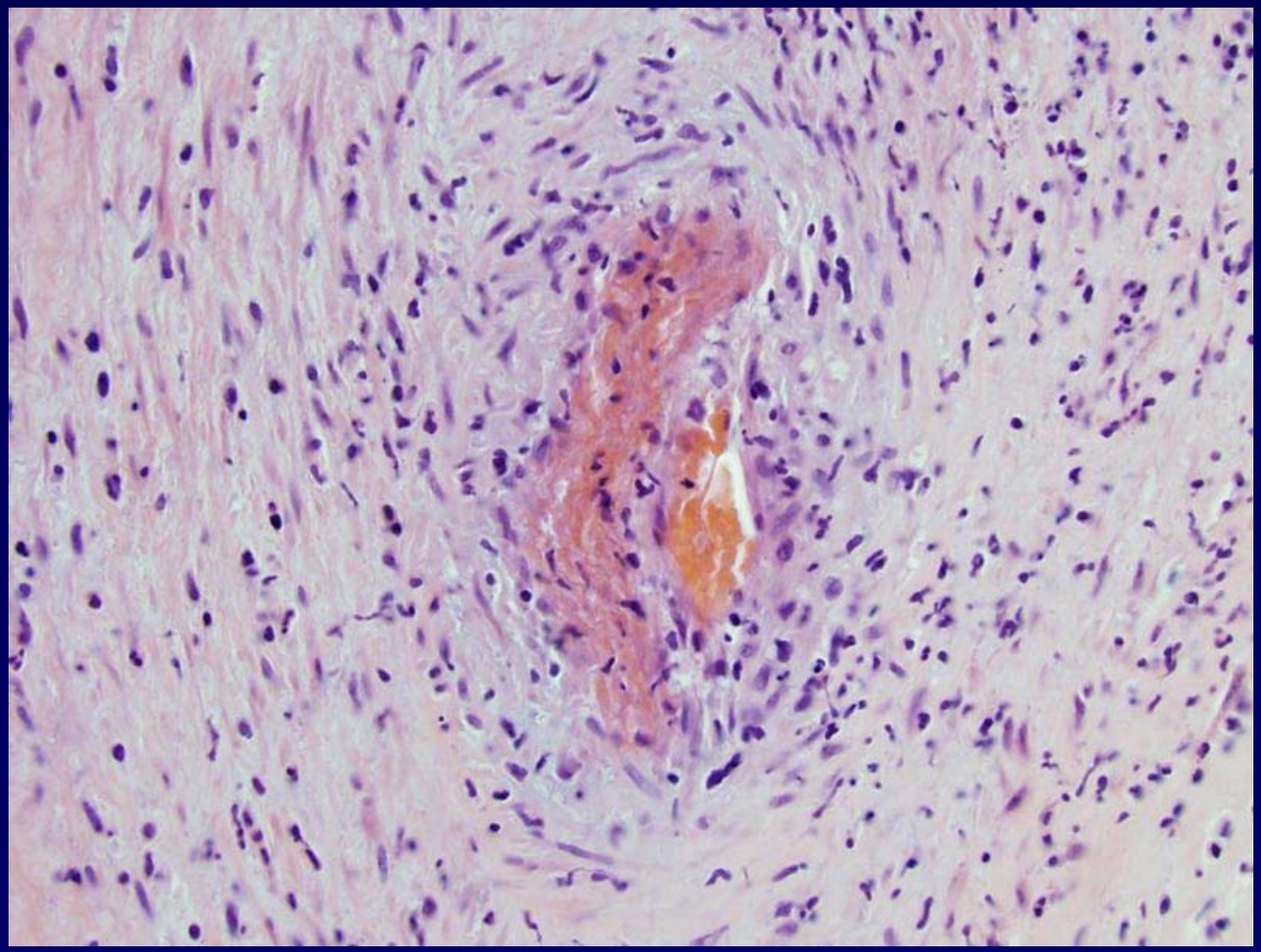
Chorionic Vasculitis with Thrombi



Chorionic Vasculitis with Thrombi



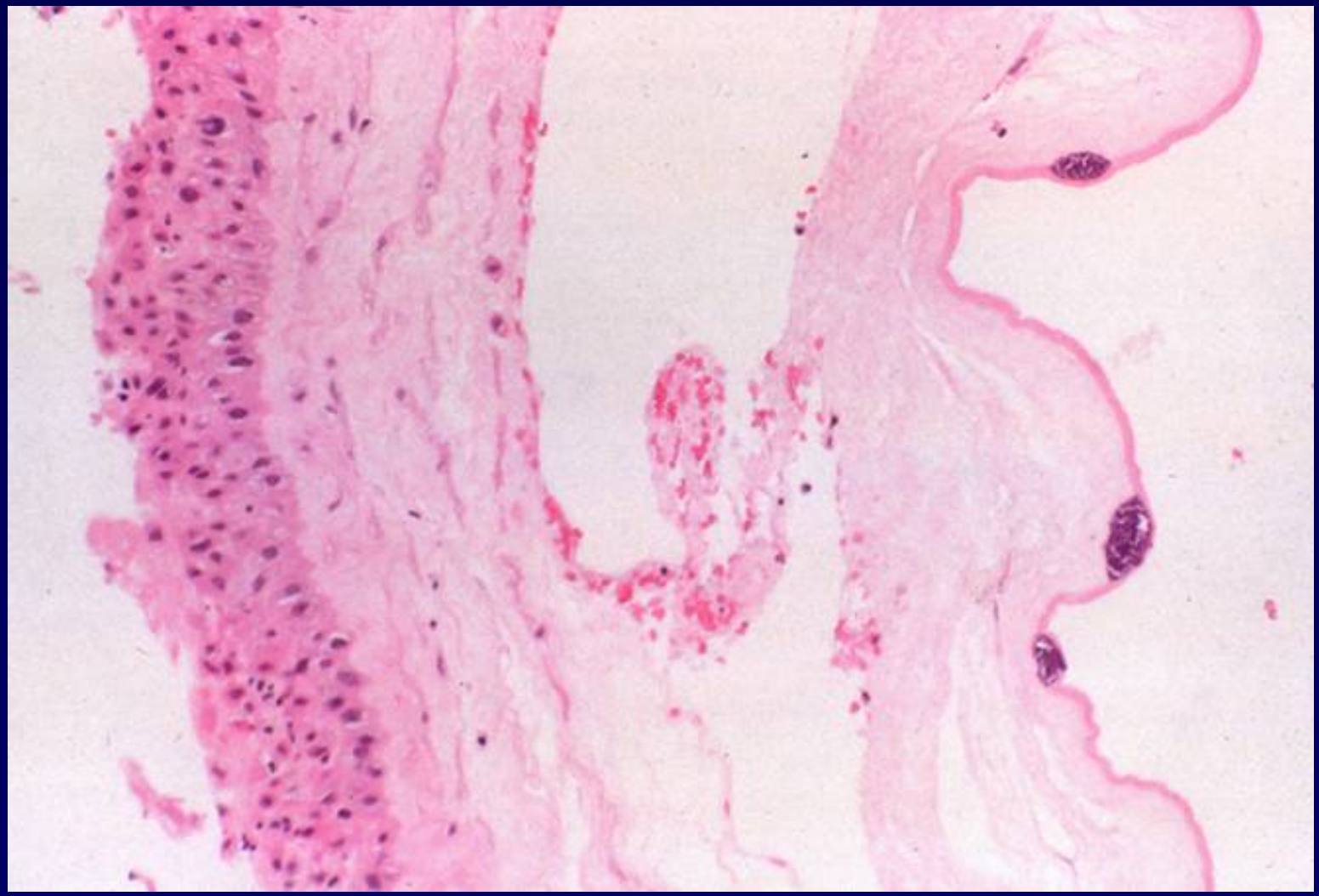
Chorionic Vasculitis with Thrombi



Ascending Infection

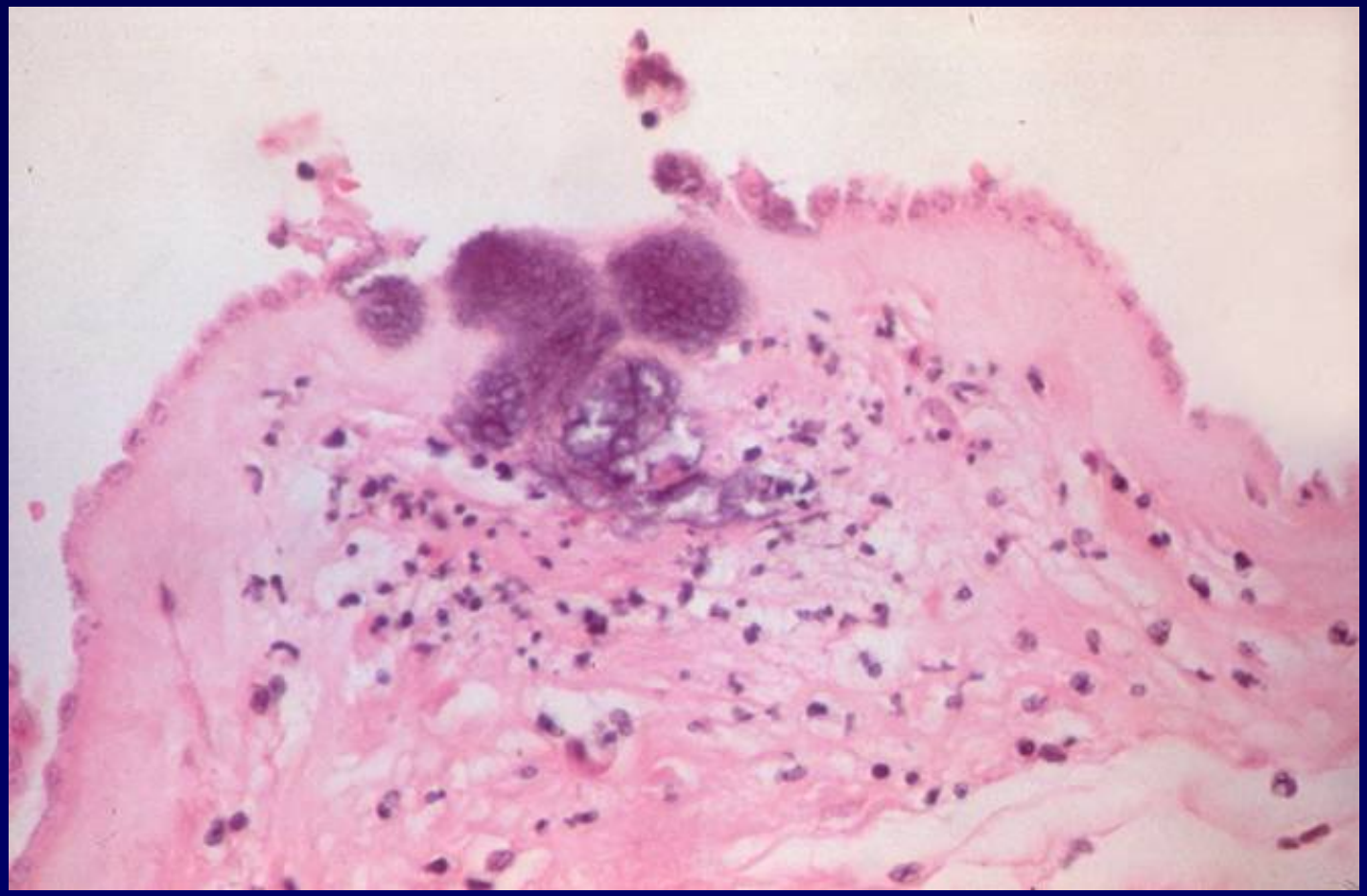
- Rarely see causative organisms in sections
- Exceptions:
  - Group B beta-hemolytic *streptococcus*
  - *Fusobacterium*
  - *Candida*

Group B beta-hemolytic strep



Bacterial colonies with no inflammatory response

Group B beta-hemolytic strep

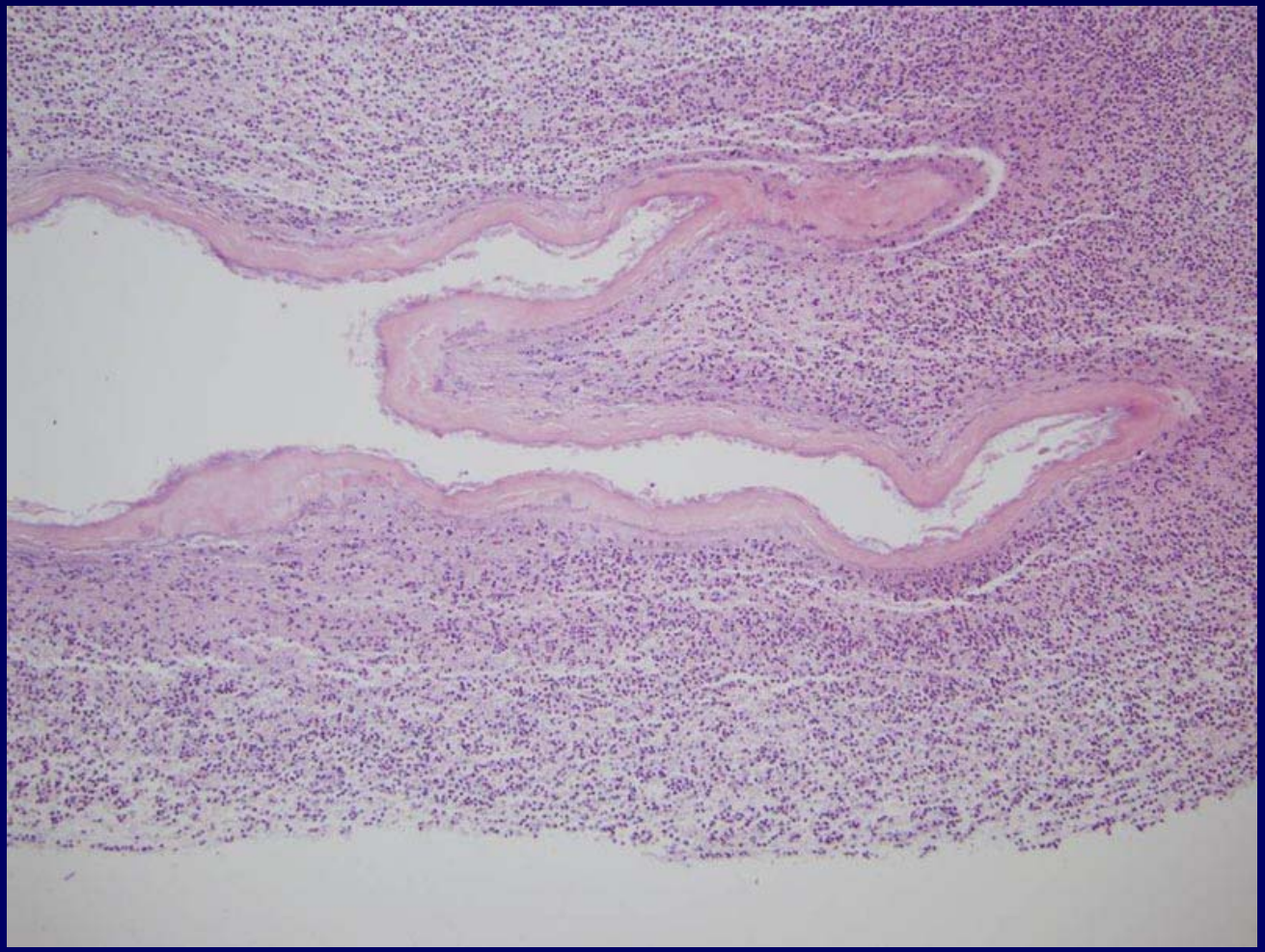


Bacterial colonies

Case 4
Fusobacterium Acute Chorioamnionitis

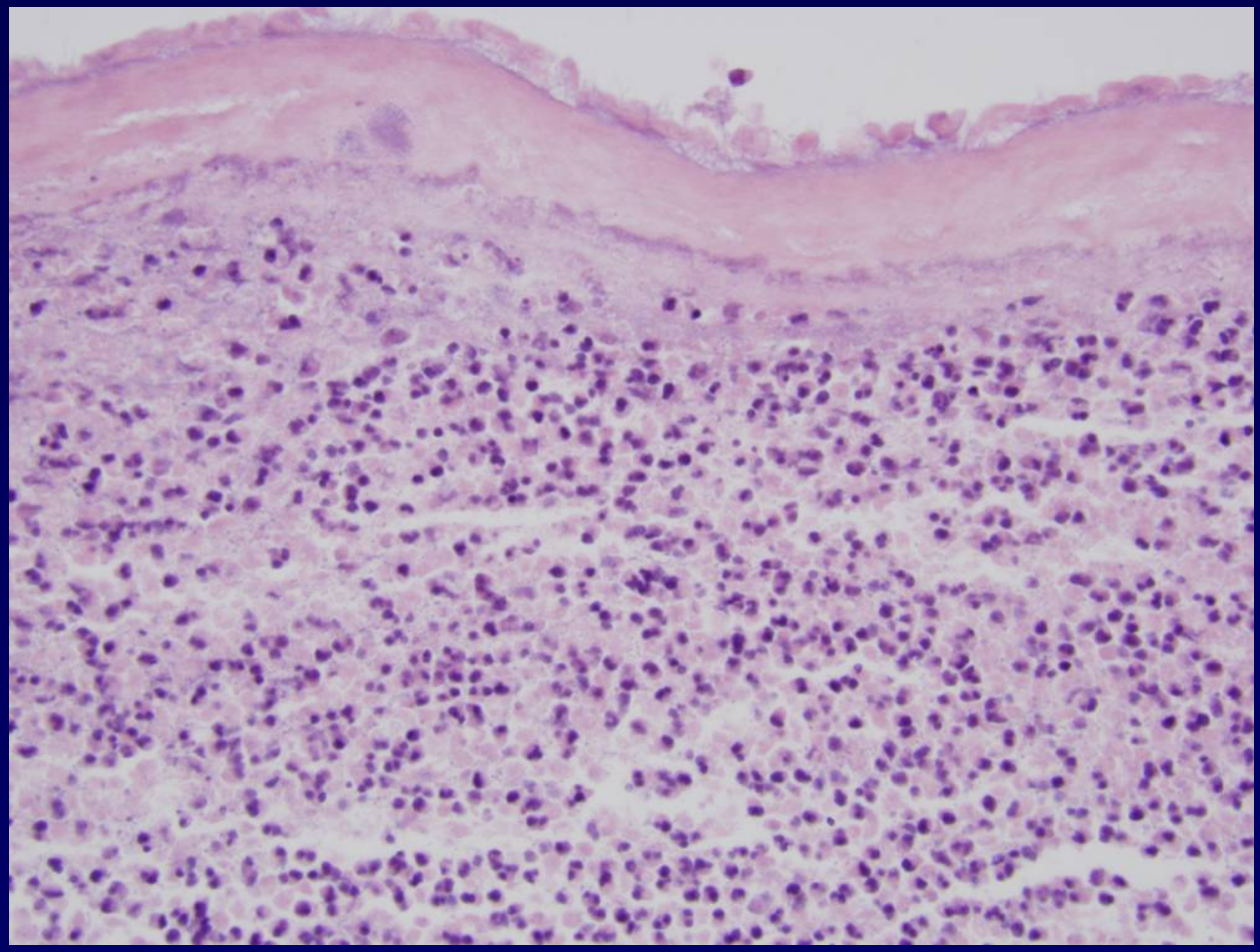
This 25 year old G1 woman presented with a nonviable intrauterine pregnancy at 21 weeks gestational age.

Fusobacterium Acute Chorioamnionitis



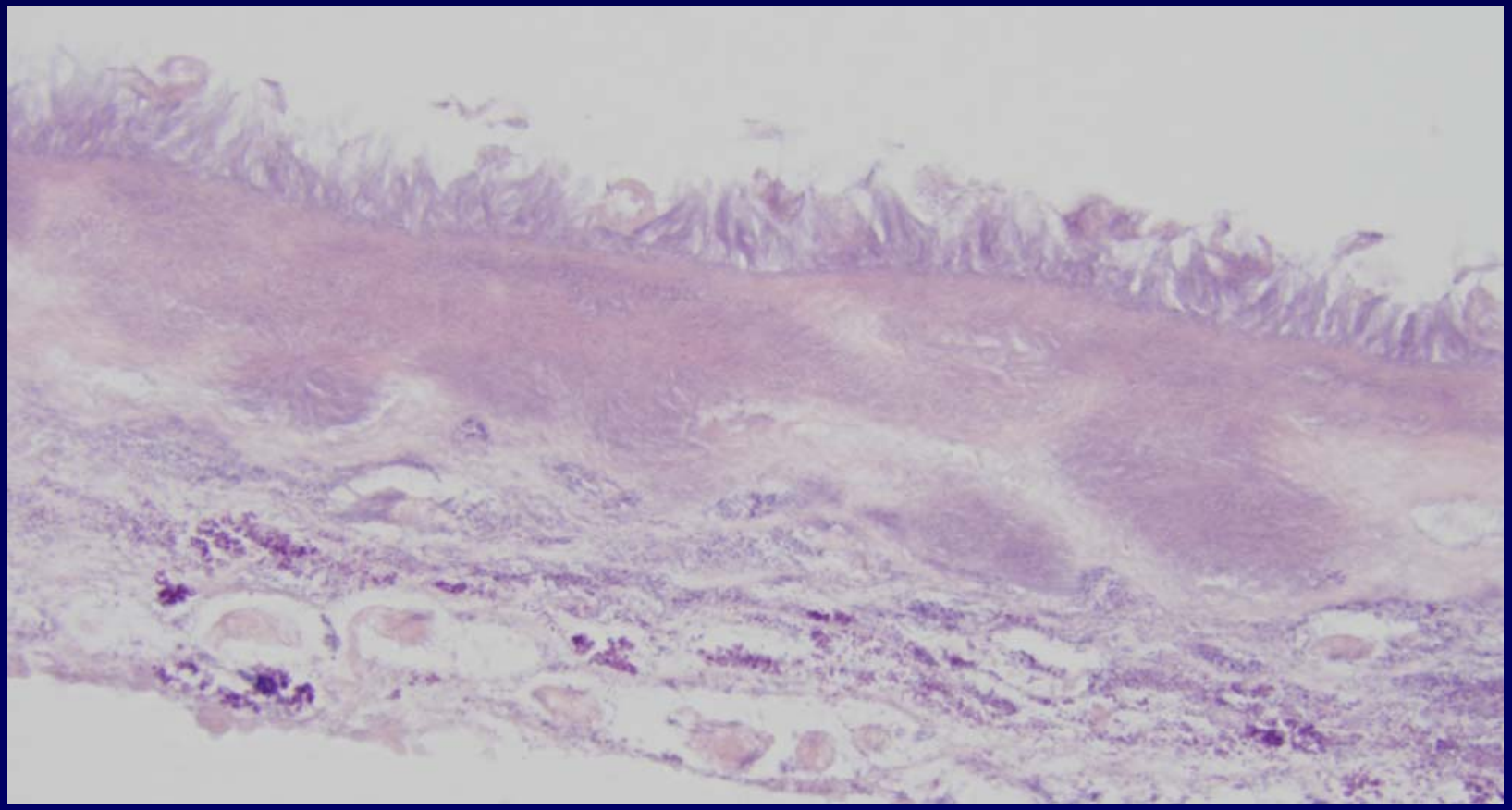
Necrotizing chorioamnionitis, severe (stage 3 grade 2)

Fusobacterium Acute Chorioamnionitis



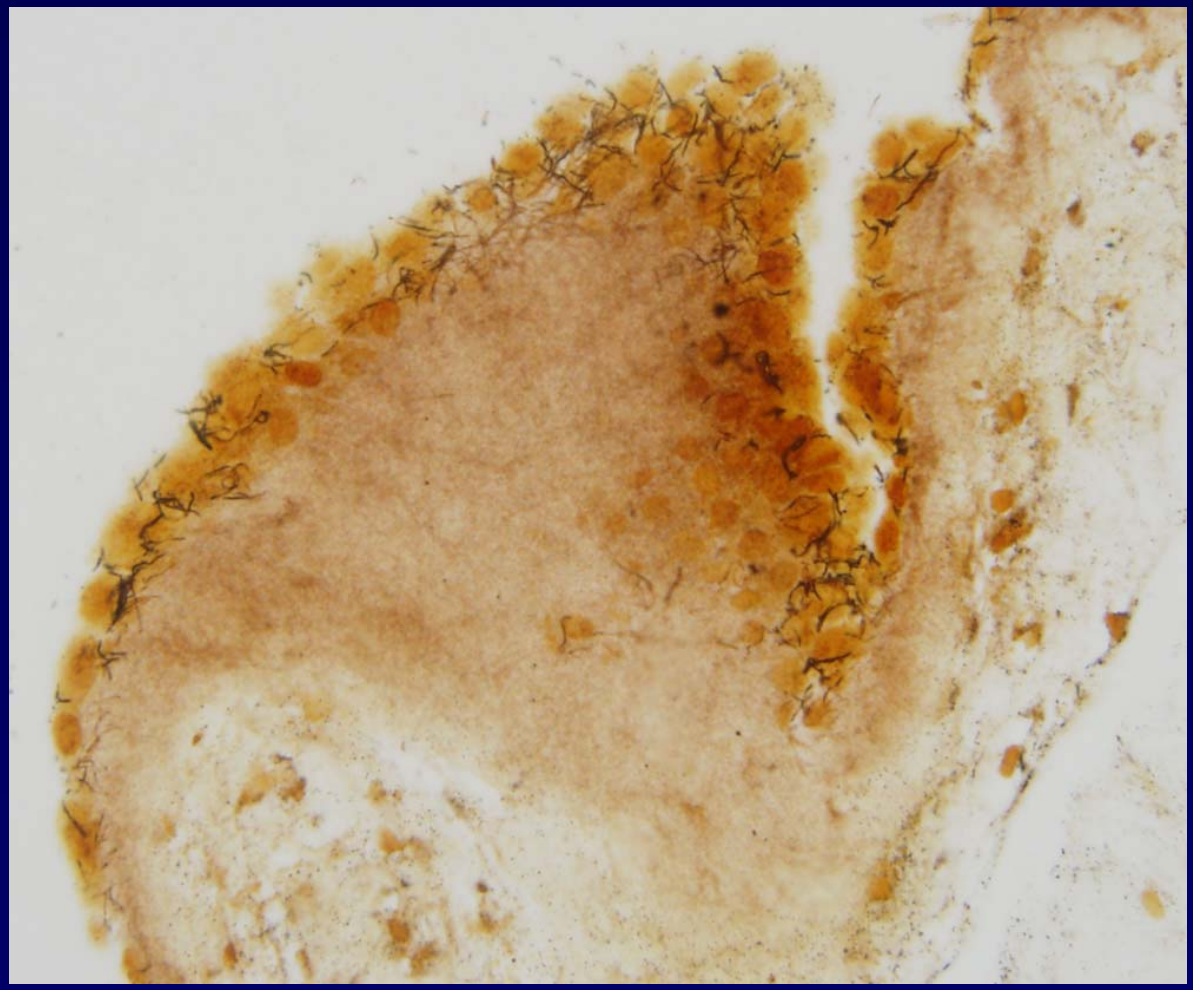
Necrotizing chorioamnionitis, severe - stage 3, grade 2

Fusobacterium Acute Chorioamnionitis



Collections of long, thin, organisms

Fusobacterium Acute Chorioamnionitis



Fusobacterium Chorioamnionitis

Fusobacterium nucleatum

- Cultured in amniotic fluid of 10 to 30% of women in preterm labor with intact membranes
- Cultured in amniotic fluid of 10% with preterm labor and ruptured membranes
- Rarely cultured from lower genital tract
- May not be ascending infection

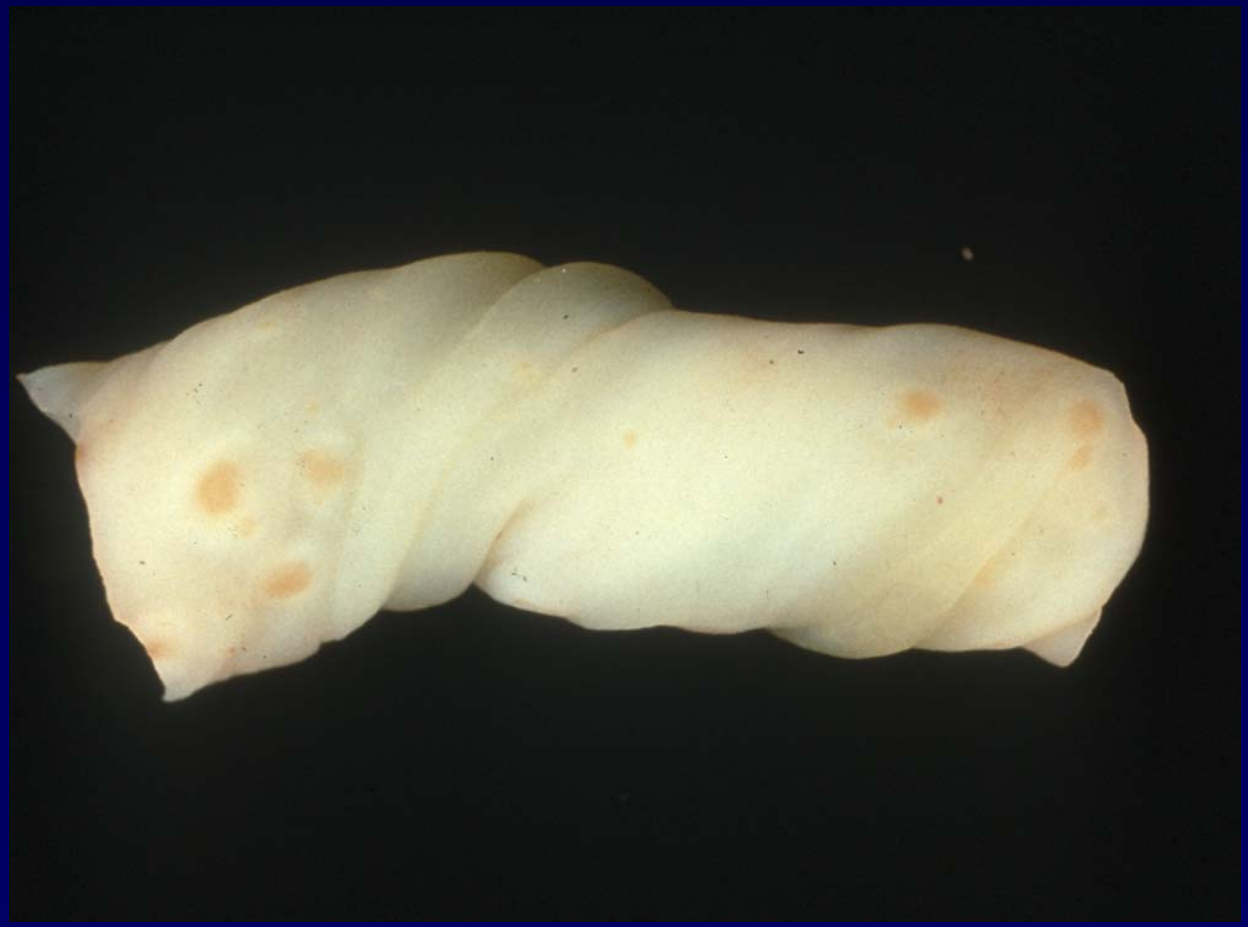
Fusobacterium Chorioamnionitis

- Ubiquitous in oral cavity
- Associated with periodontal disease
- seeding from oral plaque may colonize the amniotic cavity
- Experimental evidence:
  - Intravenous injection of *fusobacterium nucleatum* colonizes and proliferates in uterus, spreads to amniotic cavity, and causes preterm birth

Ascending Infection

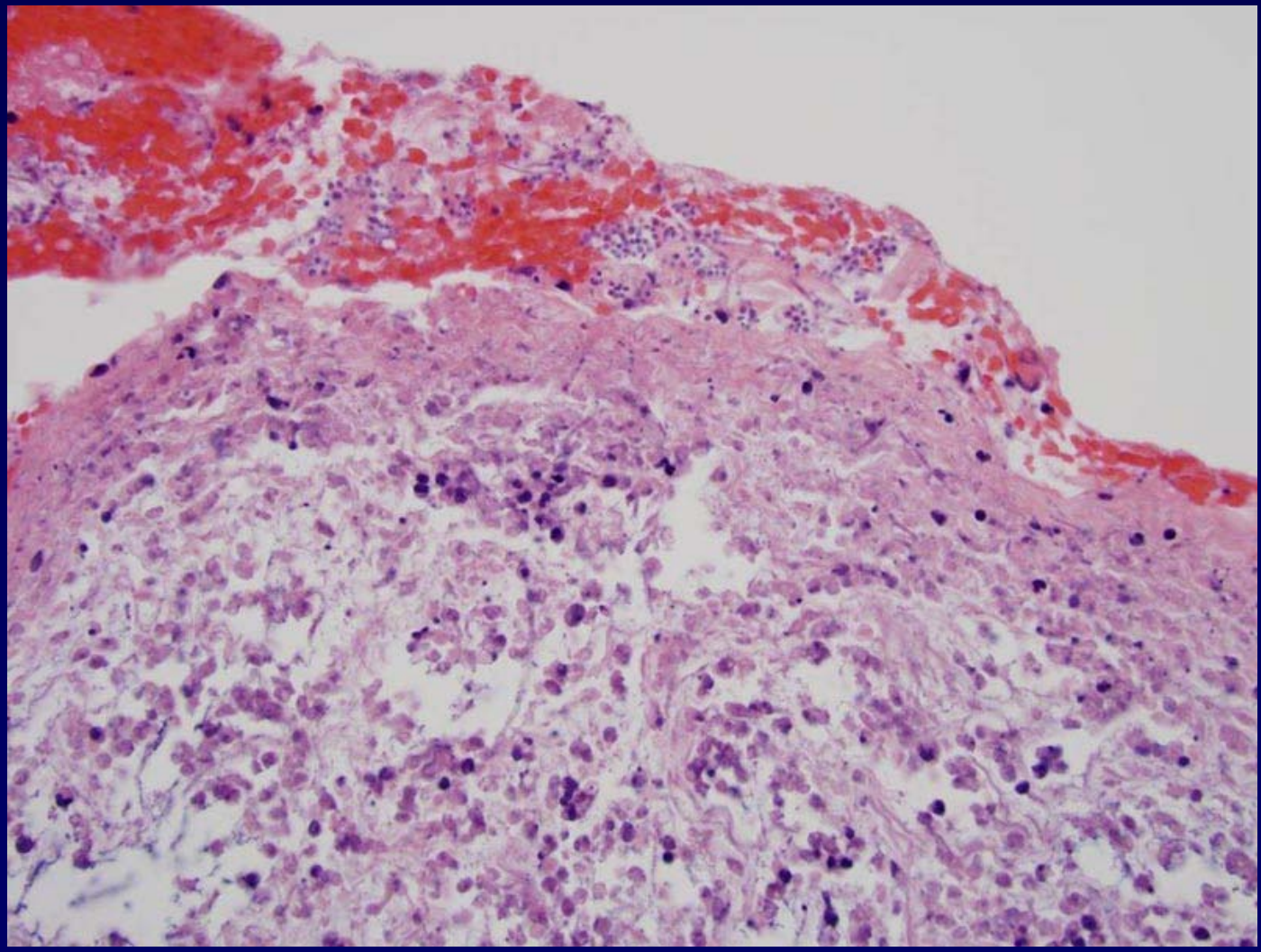
- Rarely see causative organisms in sections
- Exceptions:
  - Group B beta-hemolytic *streptococcus*
  - *Fusobacterium*
  - *Candida*

Peripheral Funisitis



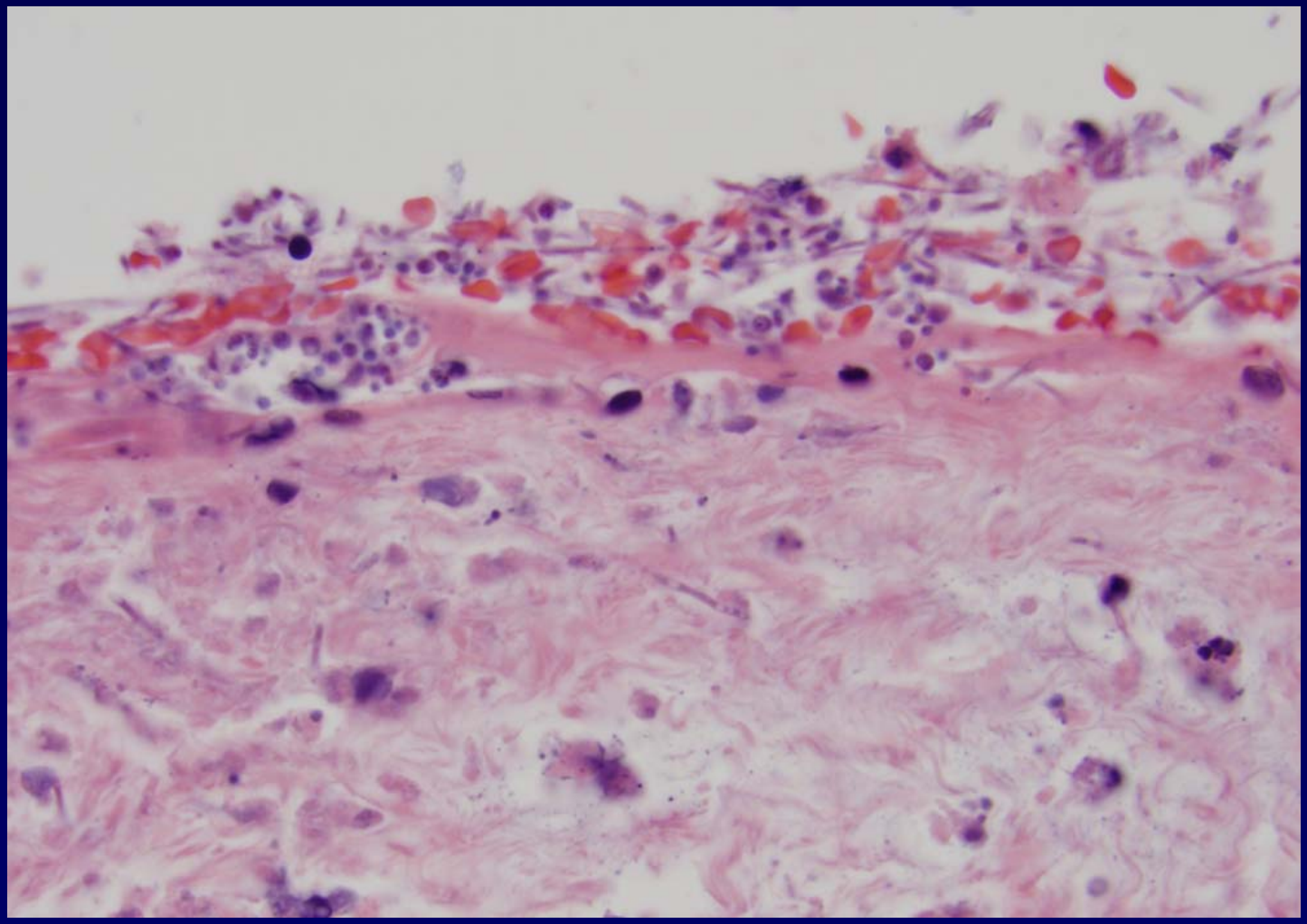
Yellow-tan plaques on cord surface

Peripheral Funisitis - Candida



Wedge-shaped collection of polys and debris on cord surface

Peripheral Funisitis - Candida

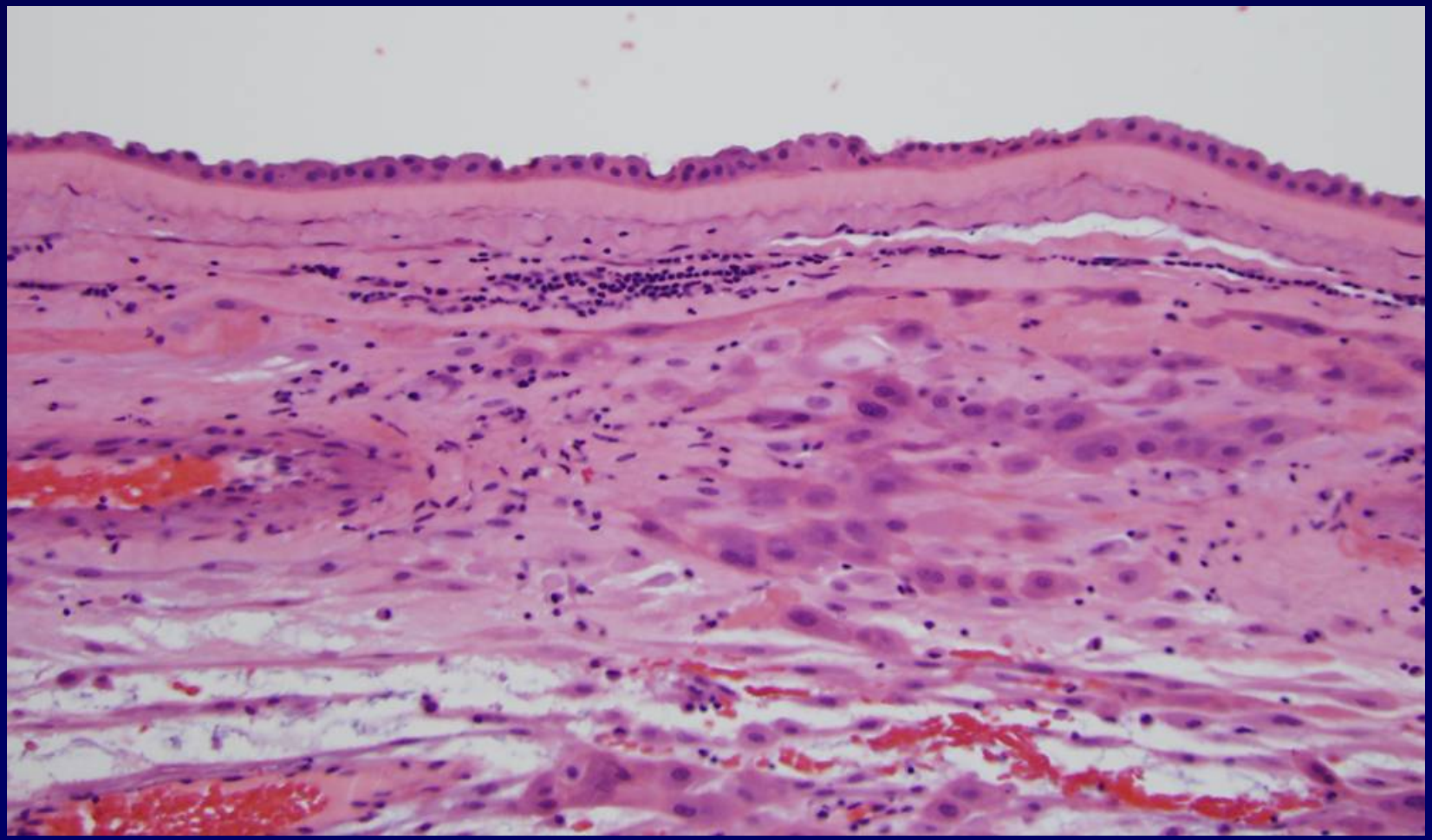


Hyphal and yeast forms are present

Ascending Infection with Candida

- If Candida funisitis
  - Usually see acute chorioamnionitis
  - May see fungal forms in membranes
- Qureshi F et al Pediatr Dev Pathol 1998;1:118-24
  - 32 cases of Candida funisitis
  - 75% premature – mean age 31 weeks
  - 16% of infants with congenital candidiasis
    - Skin rash at birth
  - Risk factors – IUD, cerclage

Chronic Chorioamnionitis



Chronic Chorioamnionitis

- See mononuclear cell infiltrate
- Often associated with chronic villitis and preterm delivery
- Rarely seen in TORCH infections

Chorioamnionitis

- At term - related to presence and duration of membrane rupture
- Preterm - likely precedes and ***causes*** membrane rupture
  - inflammatory response produces
    - prostaglandins, cytokines - trigger labor
    - metalloproteinases - weaken membrane integrity, remodel cervical tissue

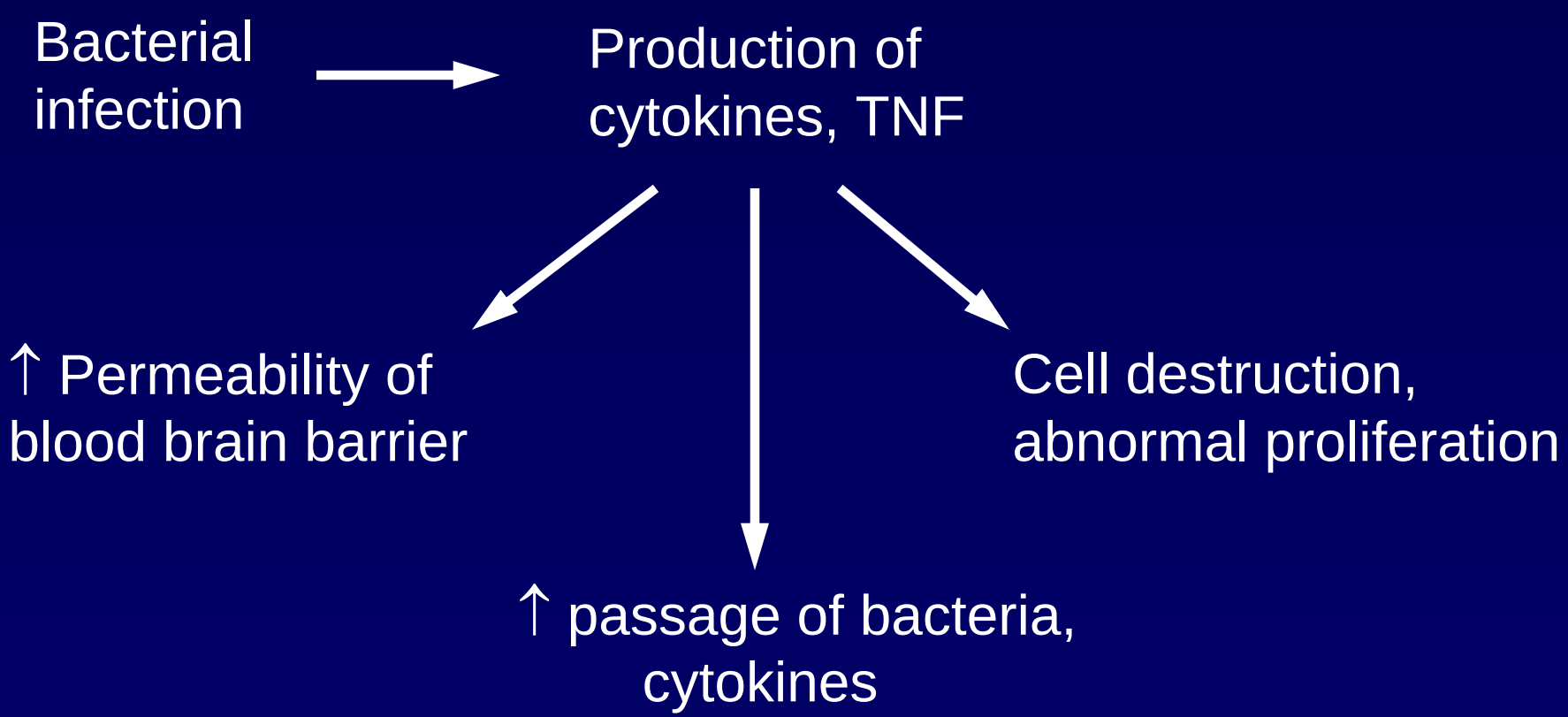
Long-term Effects of Chorioamnionitis

- Preterm birth
  - High percentage of perinatal mortality
  - High percentage of long-term neurologic morbidity
  - Chorioamnionitis is an important cause of preterm birth
  - Effects of chorioamnionitis not just due to association with prematurity

Long-term Effects of Chorioamnionitis

- Cerebral palsy is significantly associated with acute chorioamnionitis
- Fetal Inflammatory Response Syndrome
  - Intrauterine infection leads to cytokine production by fetus
  - UC IL-6 and AF IL-6 correlate with CP and periventricular leukomalacia
  - Acute funisitis, especially arteritis, may be better predictor of CP than IL-6 levels

Proposed Pathogenesis



Cerebral Palsy and Chorioamnionitis

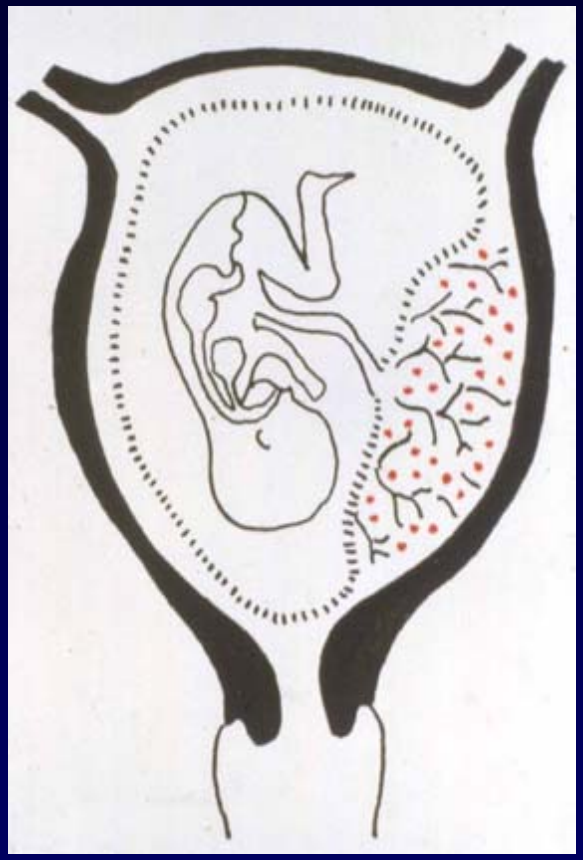
- Infection and inflammation do not explain the majority of cases
  - 82% with infection and histologic chorio do not have CP
- Other possible cofactors
  - Gestational age at time of infection
  - Intensity of fetal response
  - Genetic differences in genes that code cytokines

Long-term Effects of Acute Chorioamnionitis

Acute chorioamnionitis and funisitis are significantly associated with other types of morbidity

- Sepsis
- Respiratory distress syndrome
- Pneumonia
- Intraventricular hemorrhage
- Broncho-pulmonary dysplasia
- Necrotizing enterocolitis

Hematogenous Infection



- Virus – CMV, Rubella, Varicella, Parvovirus, HSV
- Bacteria – Treponema pallidum, Listeria
- Parasites – Toxoplasma gondii
- Unknown – > 95%, ? abnormal immune reaction

Hematogenous Infection Clinical Impact

- Spontaneous abortion – Rubella
- Fetal death in utero, stillbirth – Parvovirus
- Malformations – Rubella, Toxo
- Active infection – Toxo, CMV
- Delayed sequelae – CMV and others
    - Deafness
    - Mental retardation
    - Learning disabilities

Villitis

- Seldom seen on gross examination
- Location does not correlate with etiology
- > 95% is villitis of unknown etiology (VUE)
- Certain features do point to particular infections as the etiology

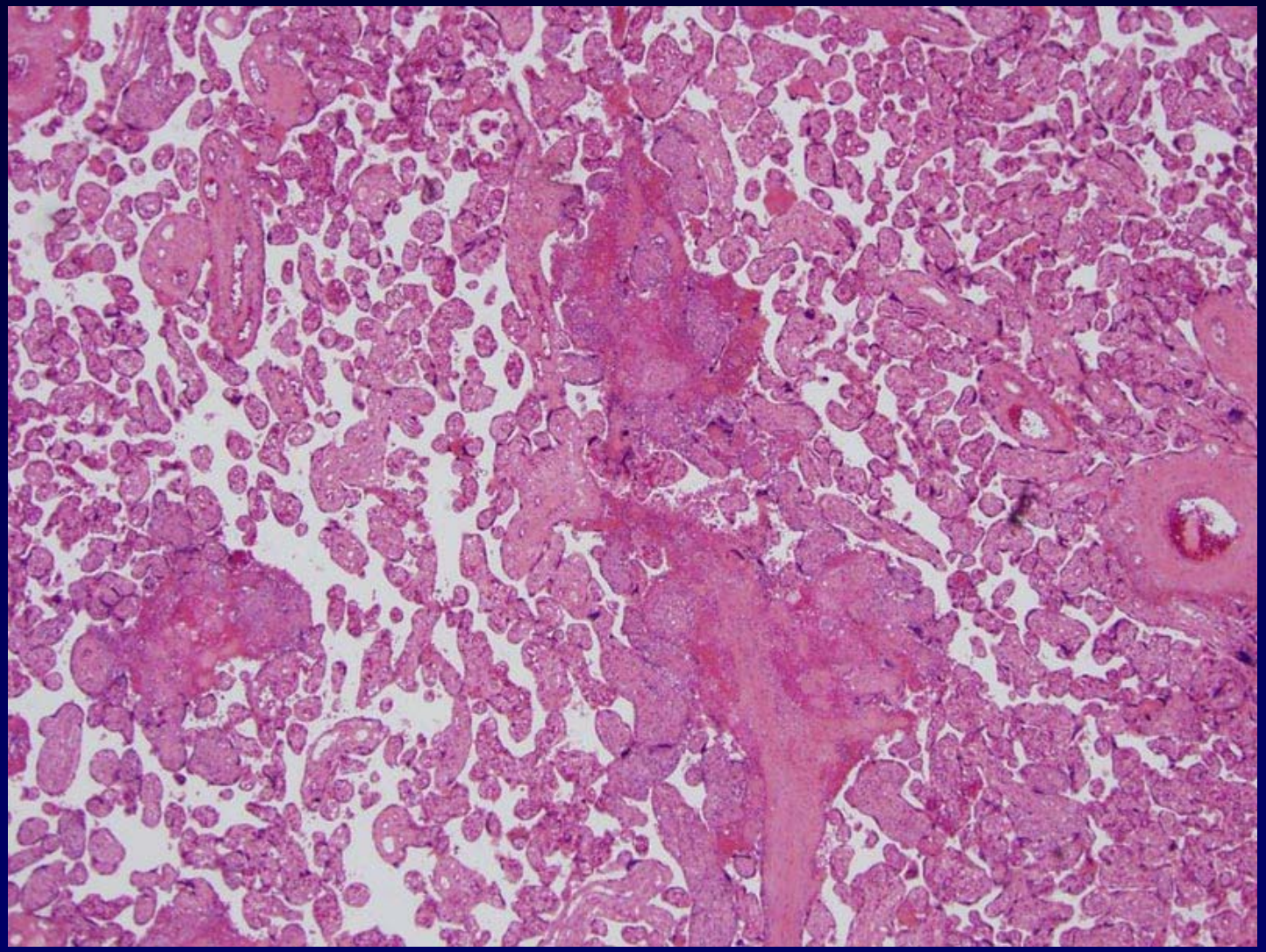
Villitis

Type	acute, chronic, granulomatous
Composition	lymphs, histiocytes, plasma cells, polys
Necrosis	necrotizing, non-necrotizing
Distribution	focal, diffuse, basal
Severity	very mild, mild, mod, severe

Villitis - Grade

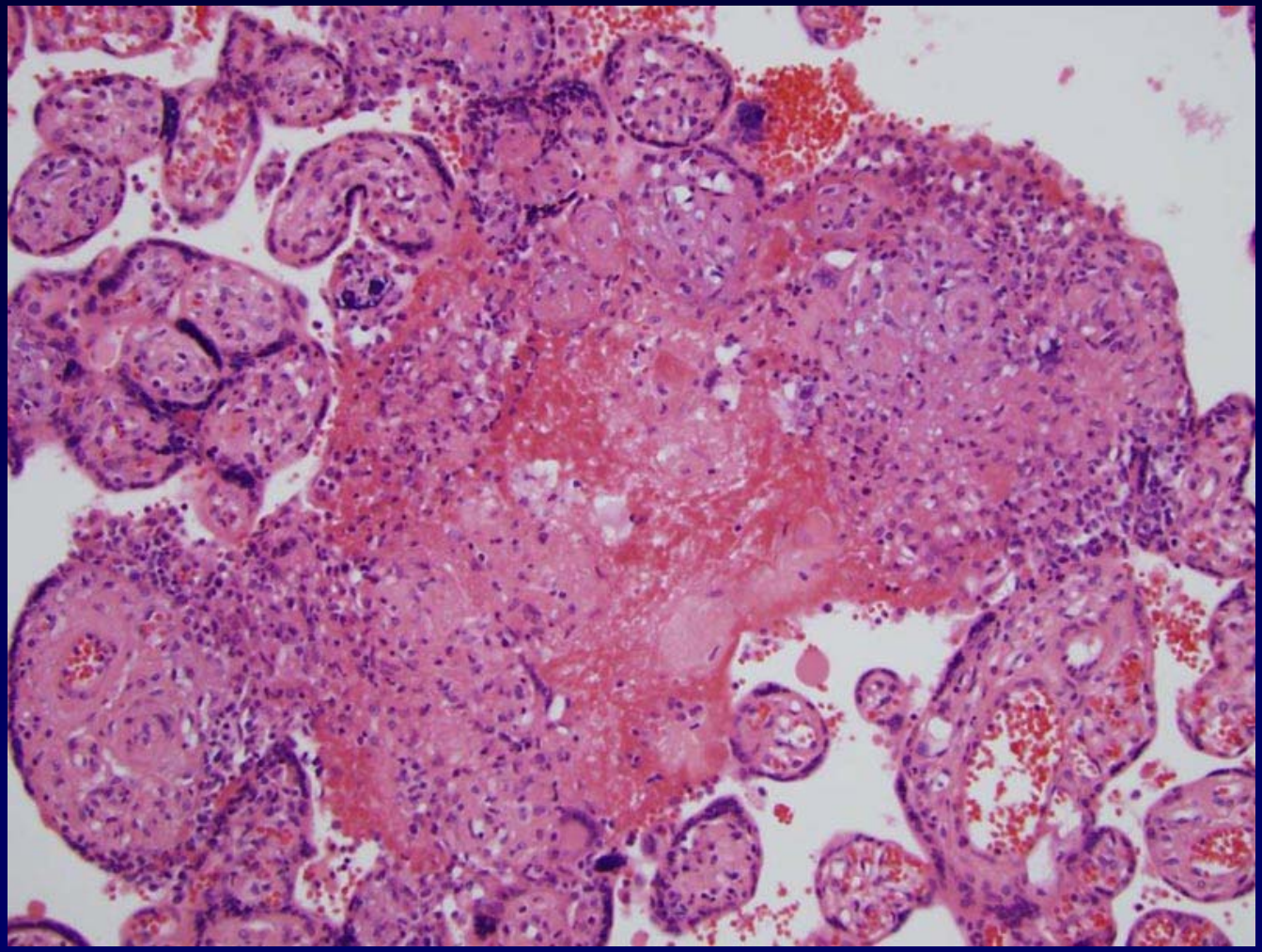
- Very mild — 1 or 2 foci each with few villi
- Mild — up to 6 foci, each up to 20 villi
- Moderate — multi foci, each up to ½ LPF
- Severe — large areas, involving most slides

Villitis



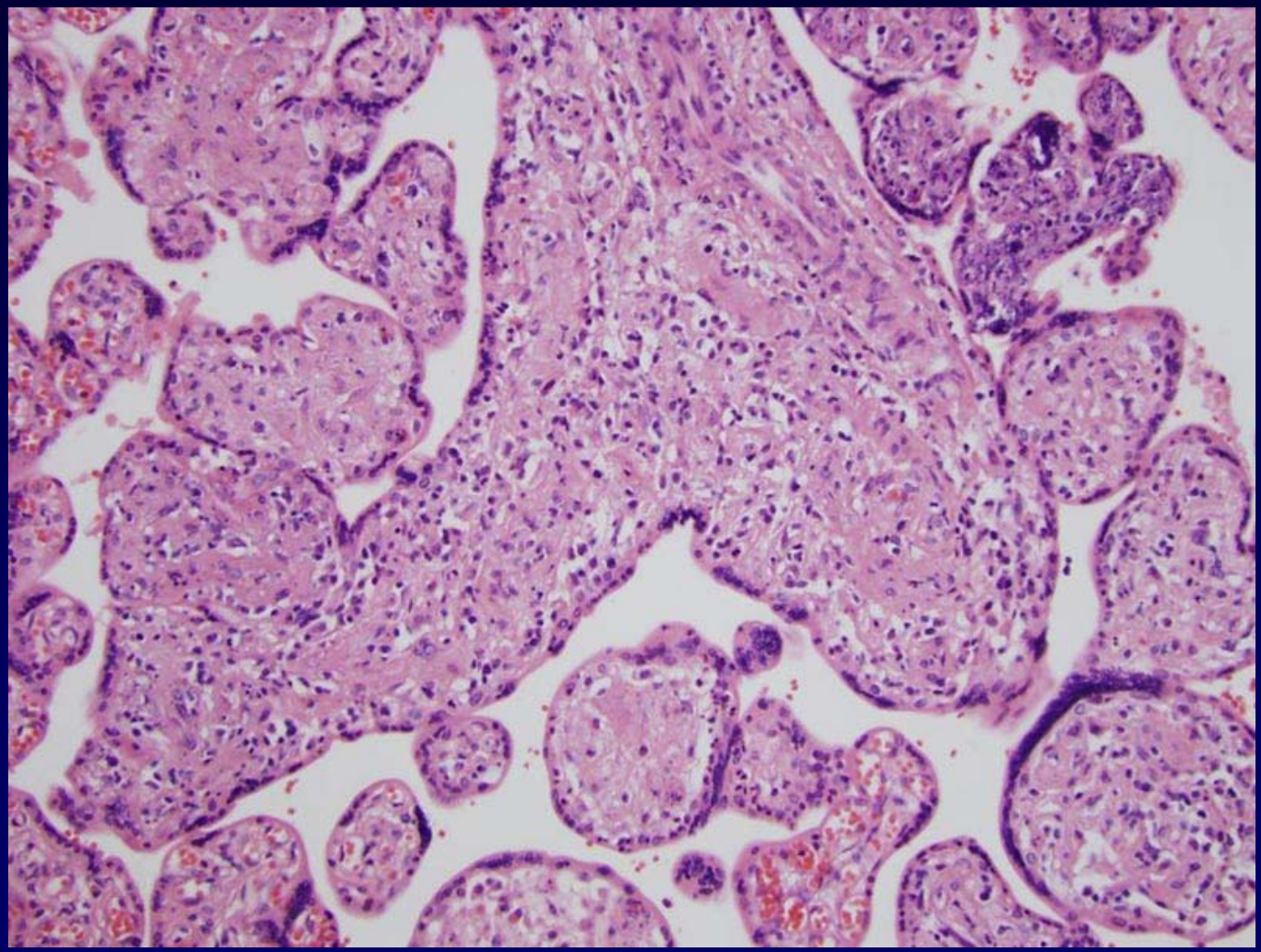
Collections of abnormally agglutinated villi

Villitis



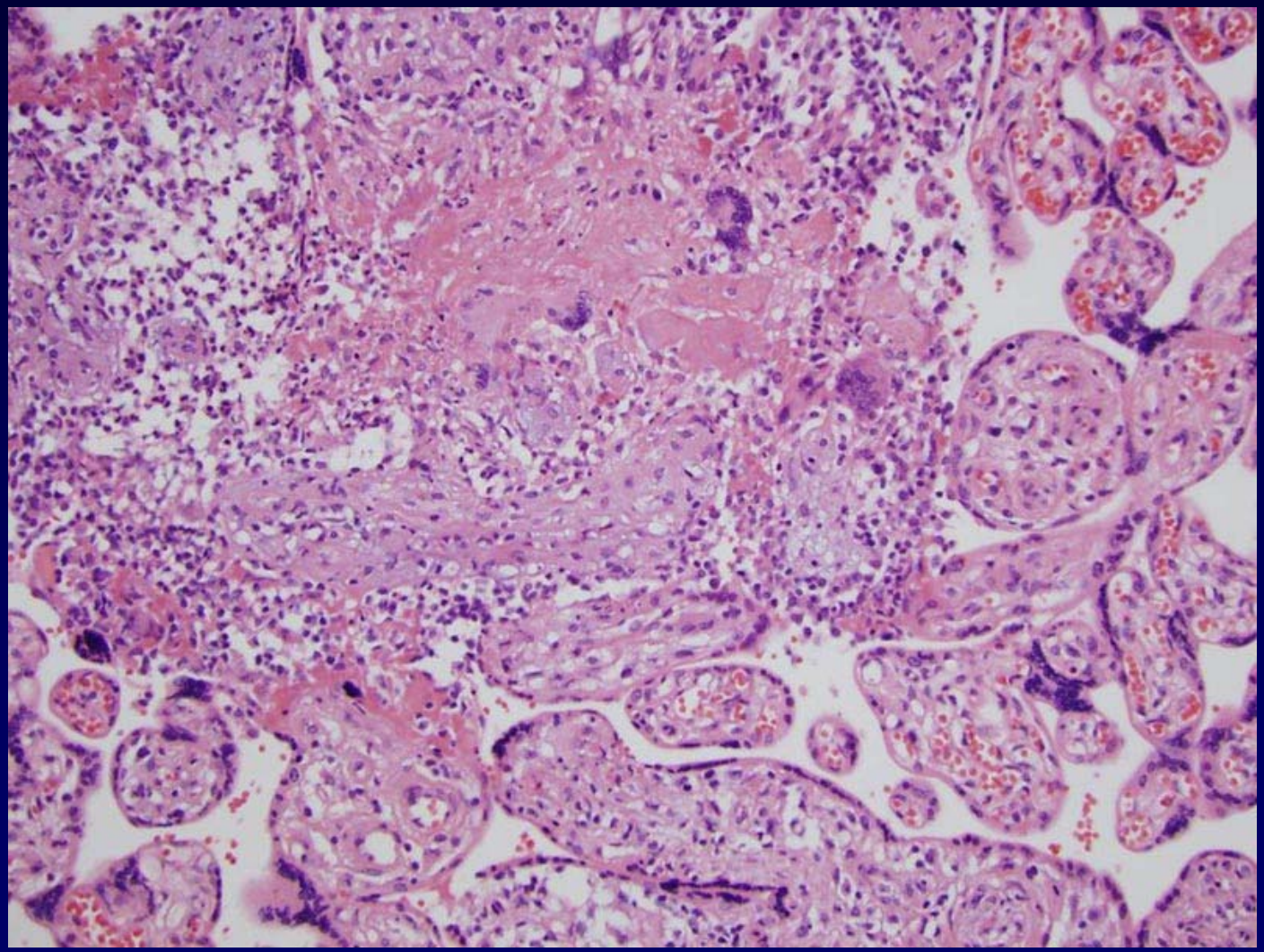
Necrotizing villitis

Villitis



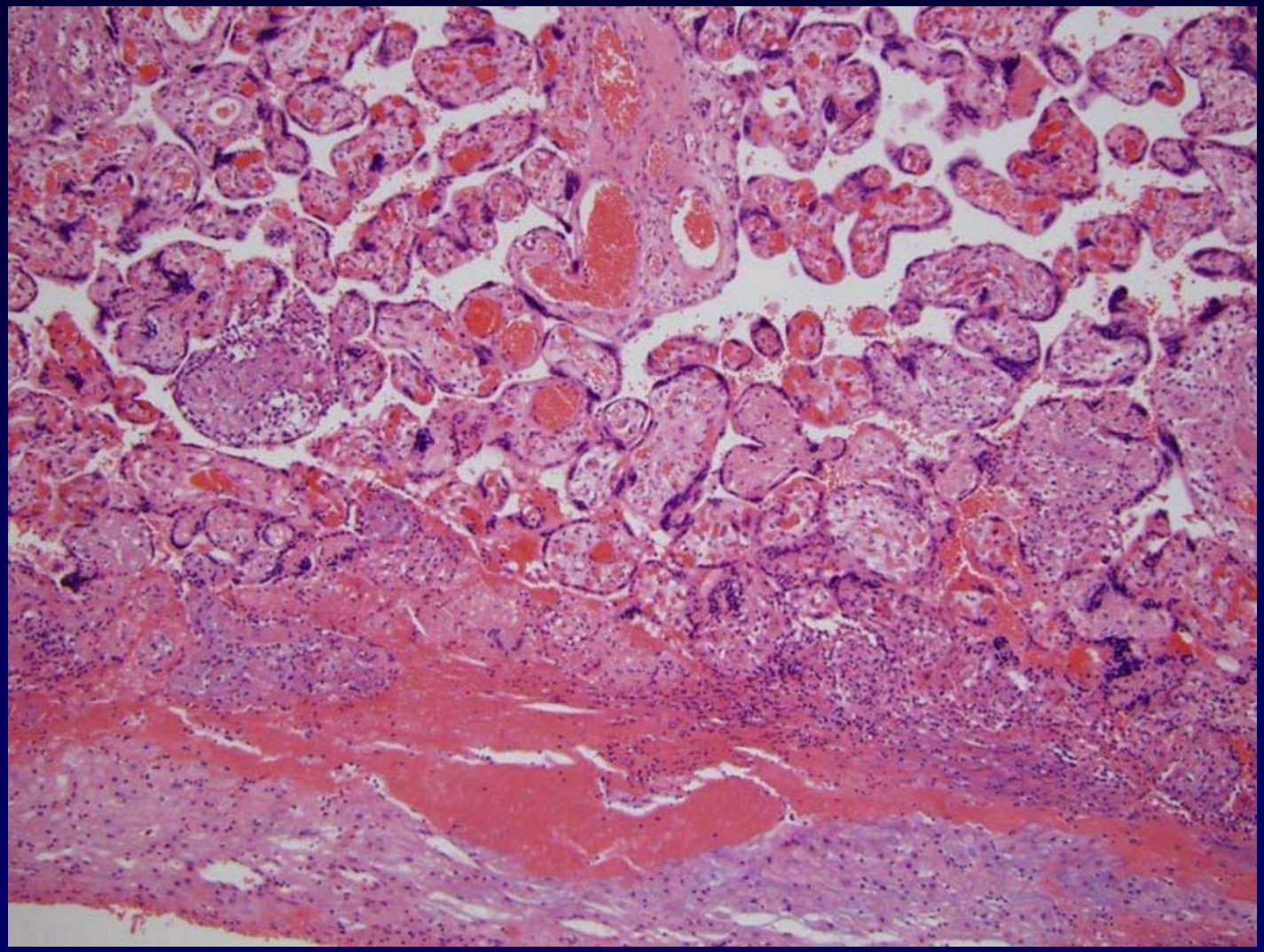
Non necrotizing villitis

Villitis



Granulomatous villitis

Villitis



Basal villitis

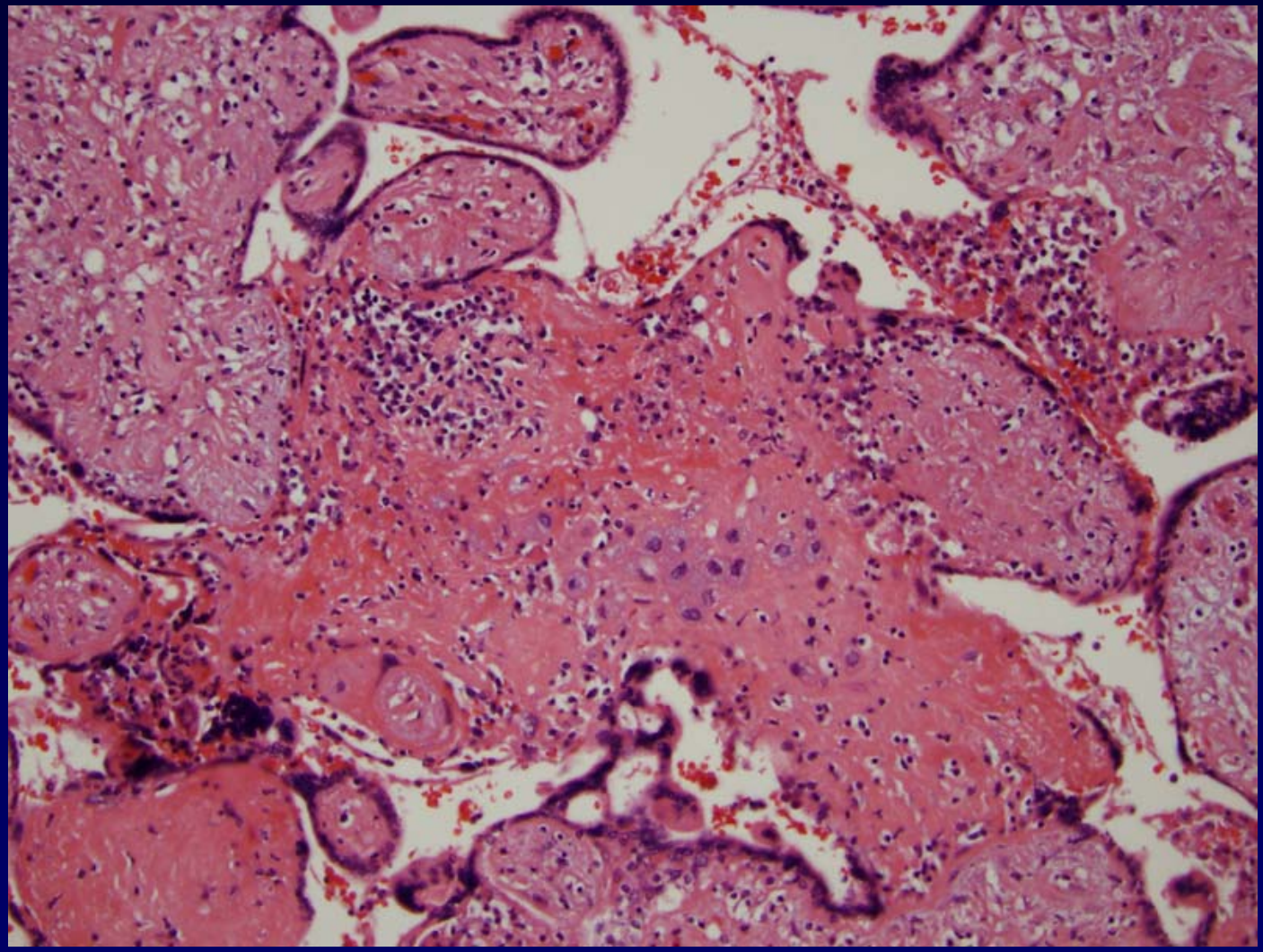
Infectious Villitis

- < 5% of all villitis
- Subtle changes suggest infection
- Confirm with
  - Special stains
  - Molecular techniques
  - Maternal/infant serology
  - Detailed clinical history

Case 5

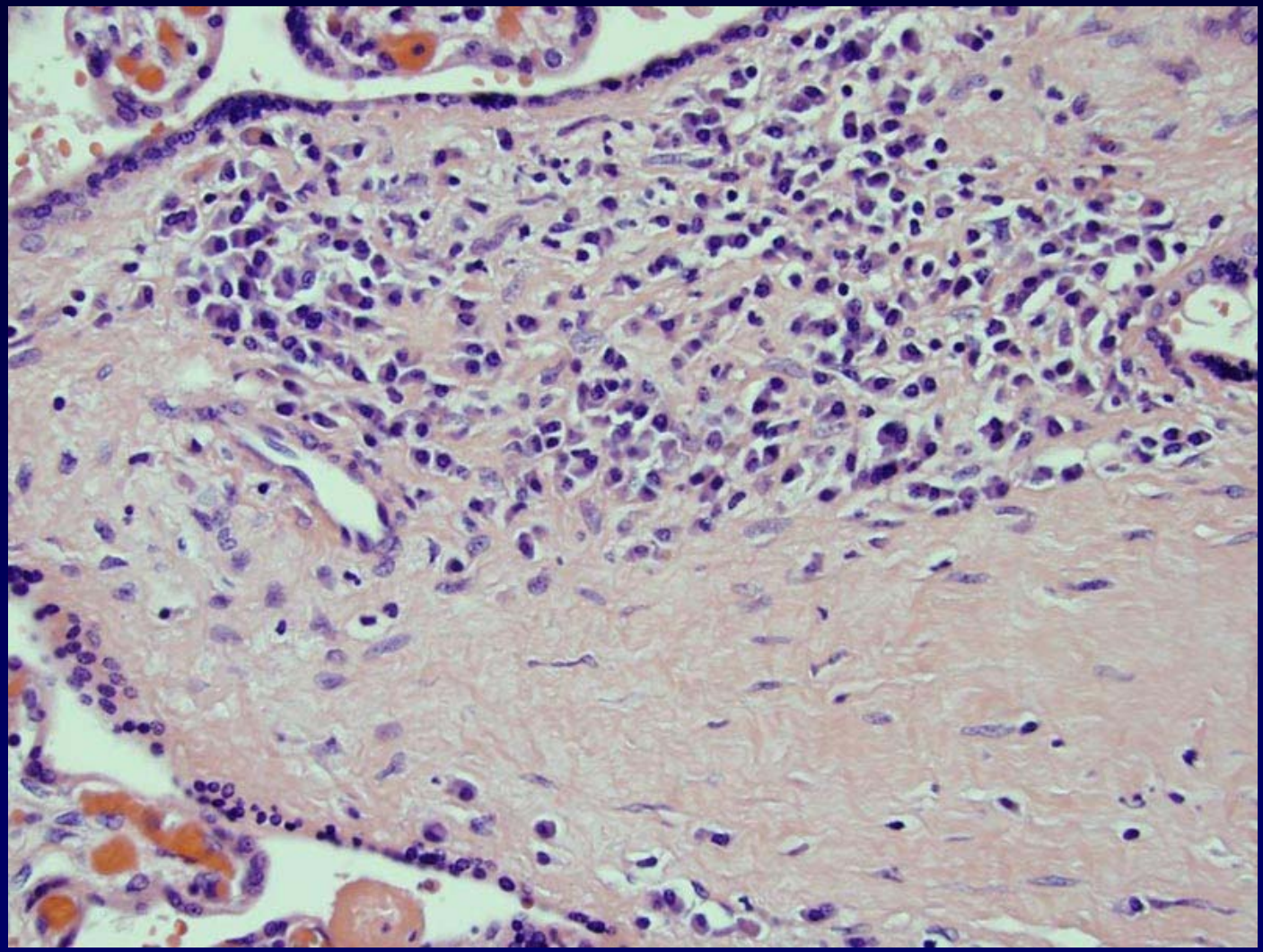
Fetal death in utero was detected at 21 weeks gestation in this 20 year old woman.

CMV



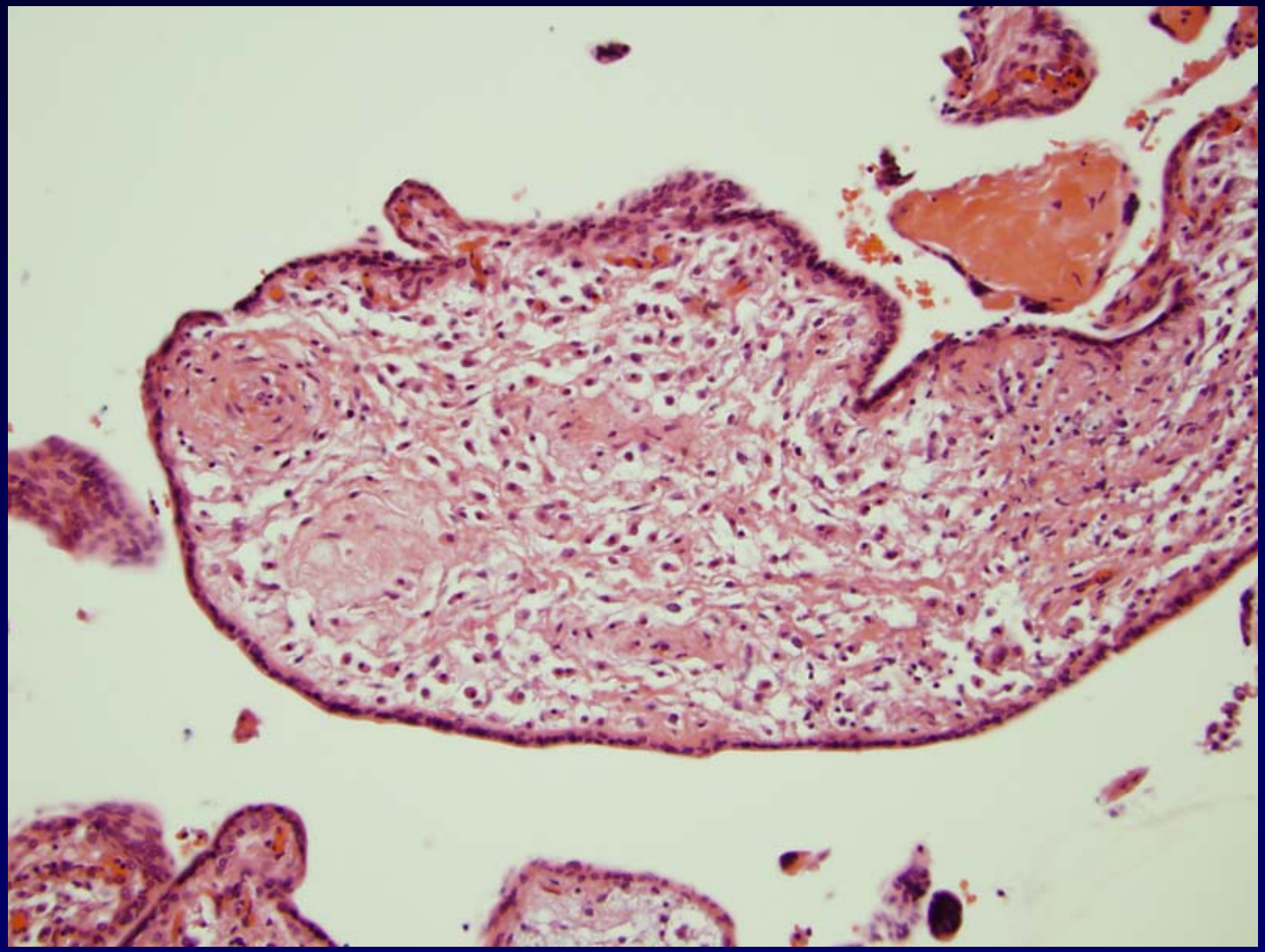
Necrotizing villitis

CMV



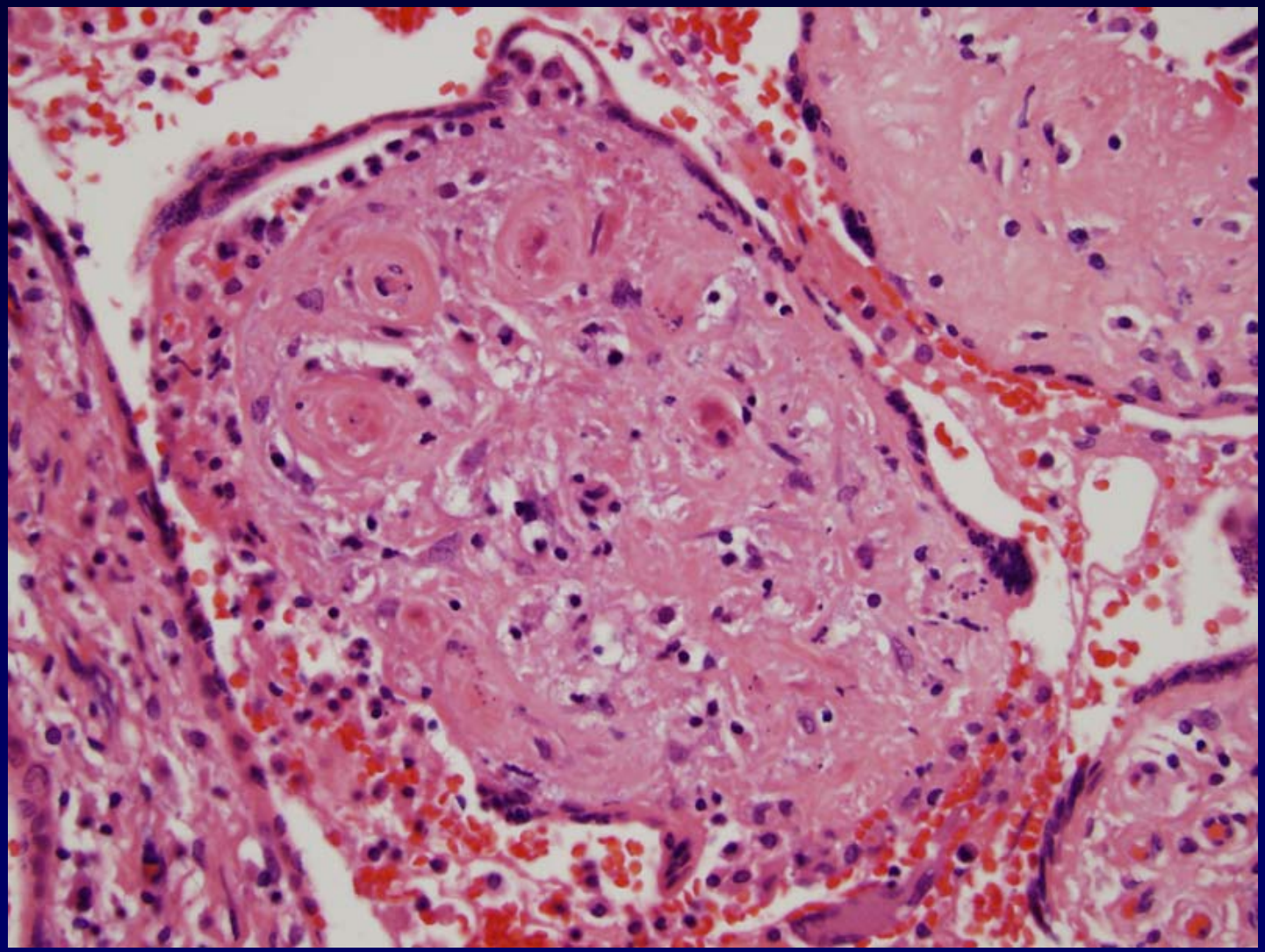
Numerous plasma cells – important clue to CMV

CMV



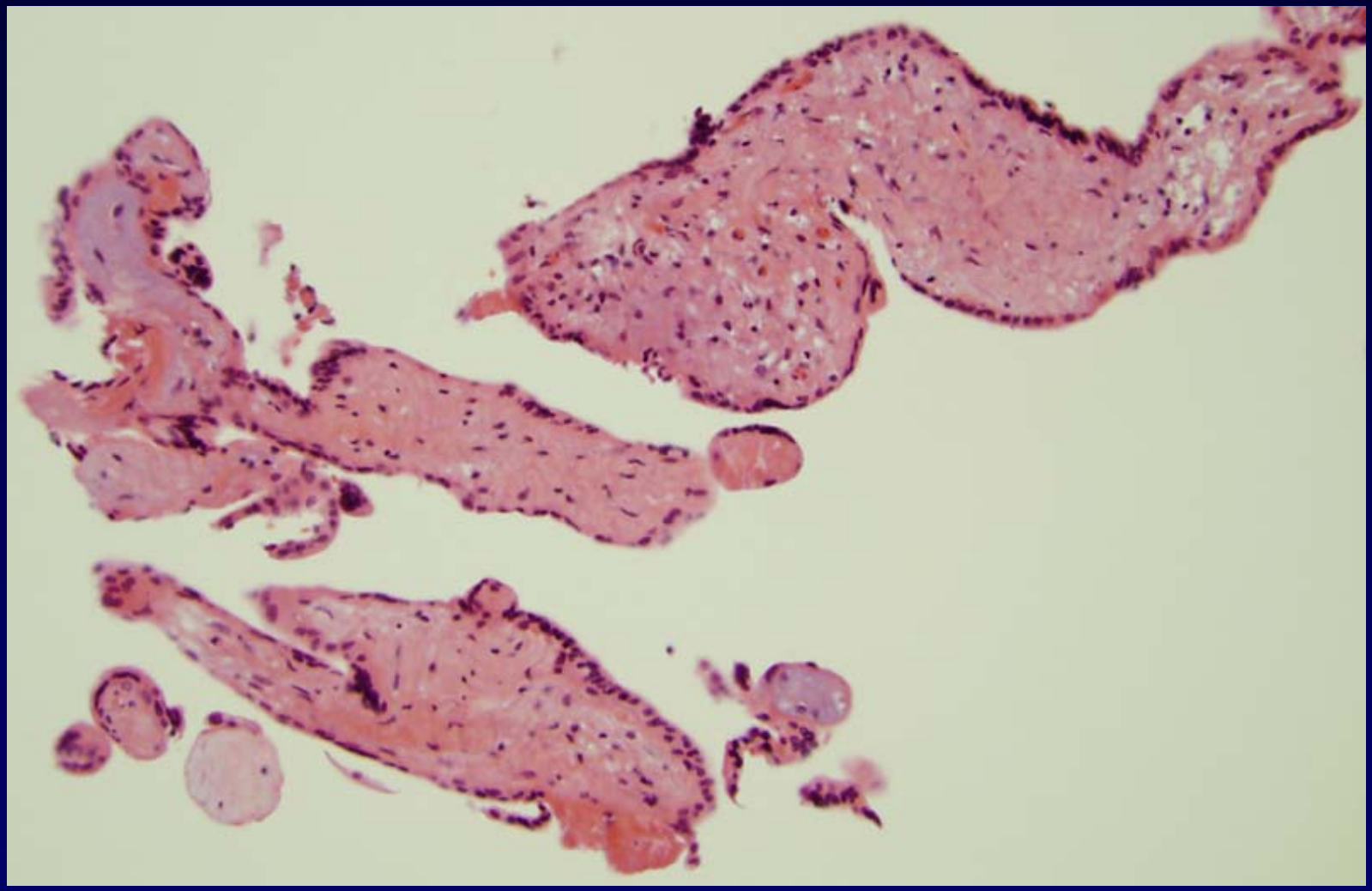
Vascular sclerosis

CMV



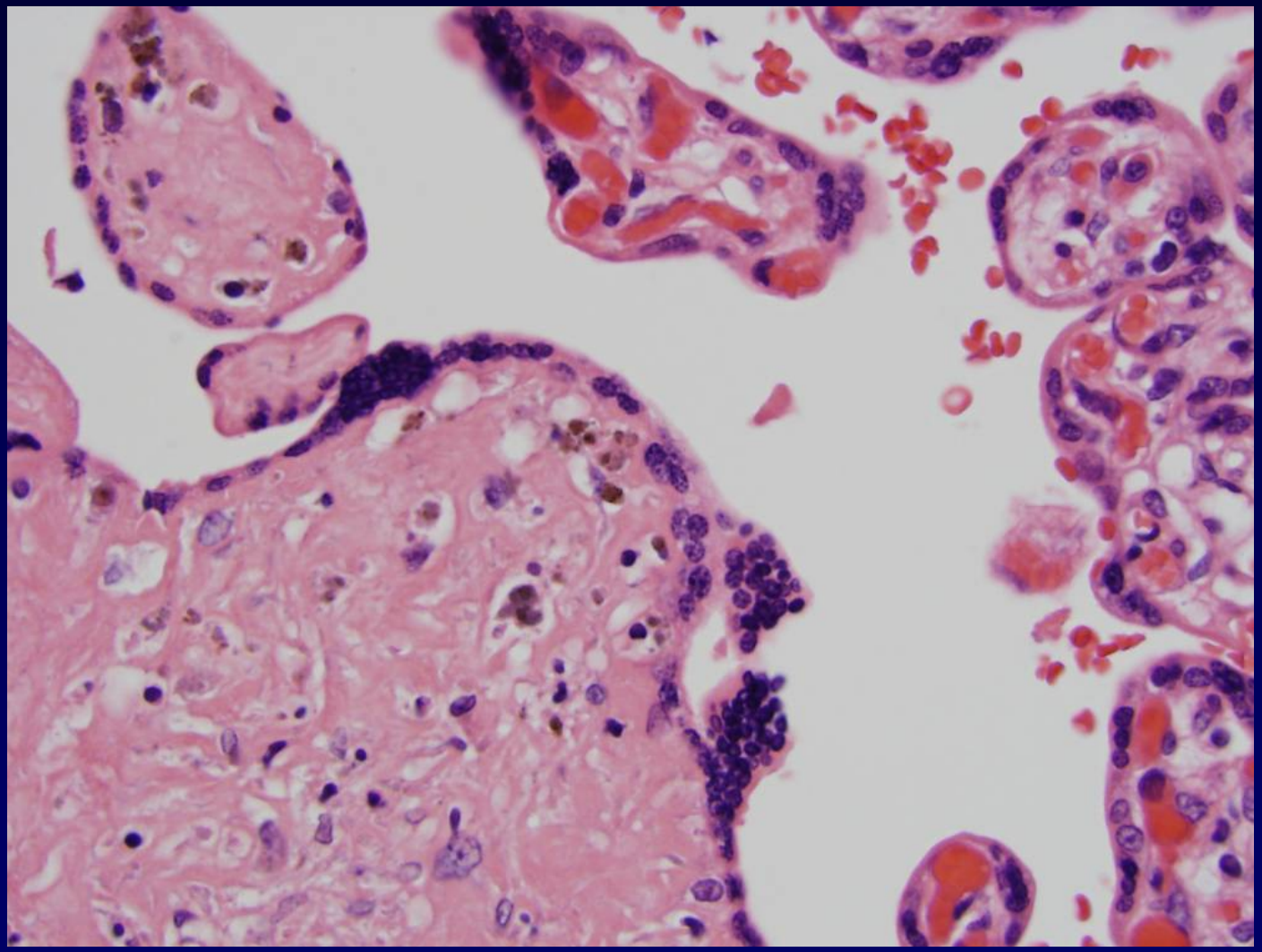
Vascular sclerosis

CMV



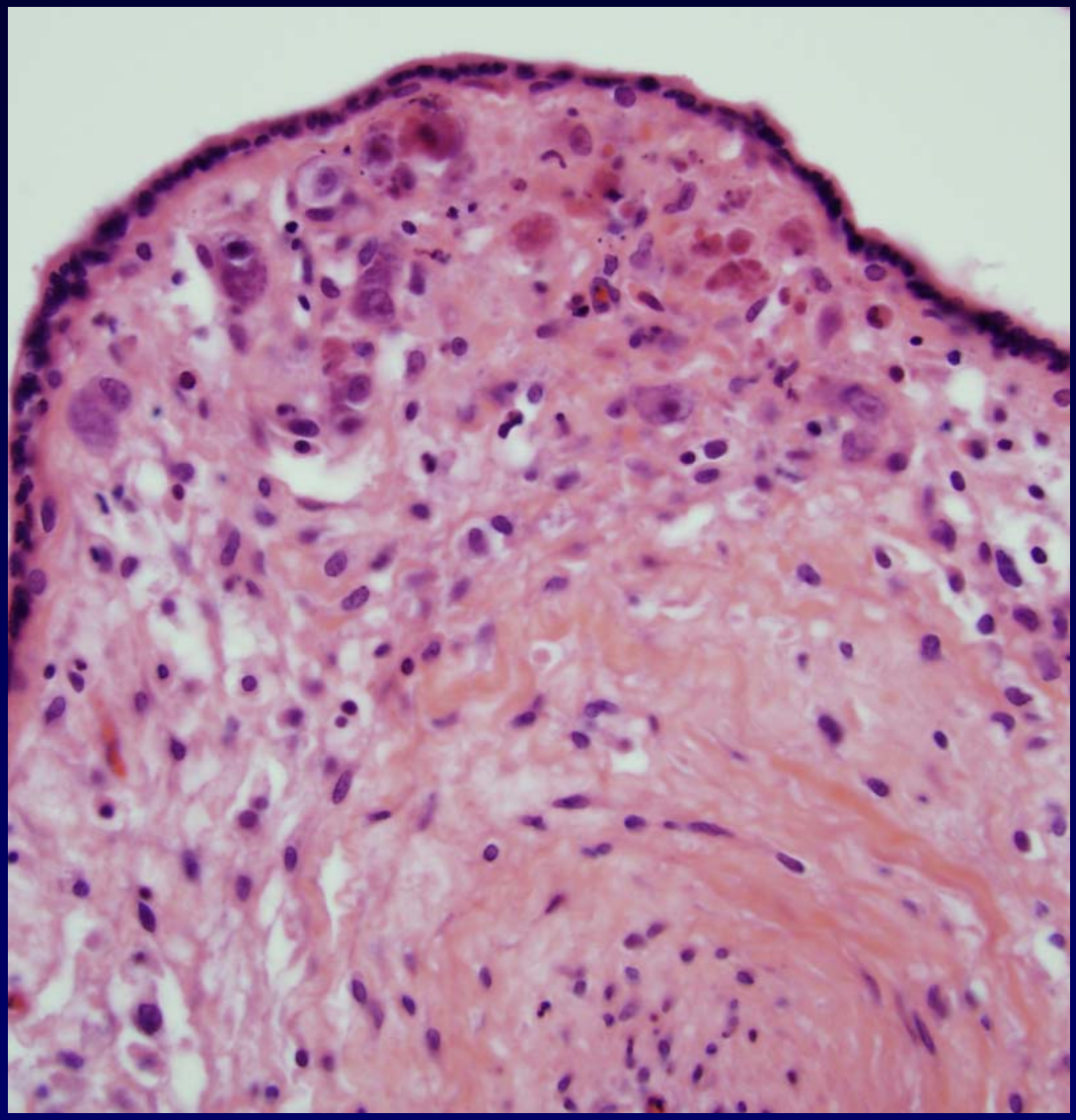
Stromal sclerosis

CMV



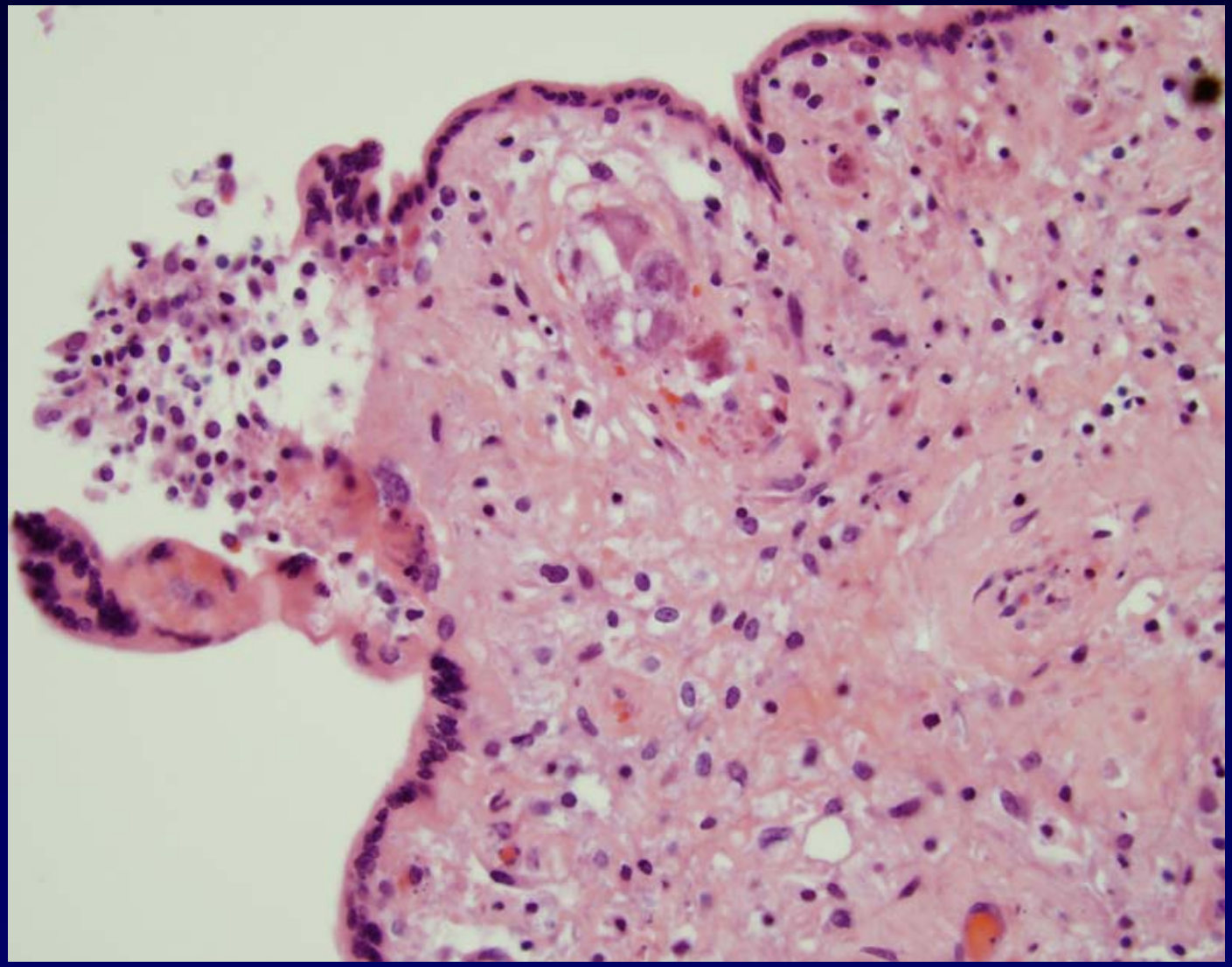
Stromal hemosiderin and sclerosis

CMV



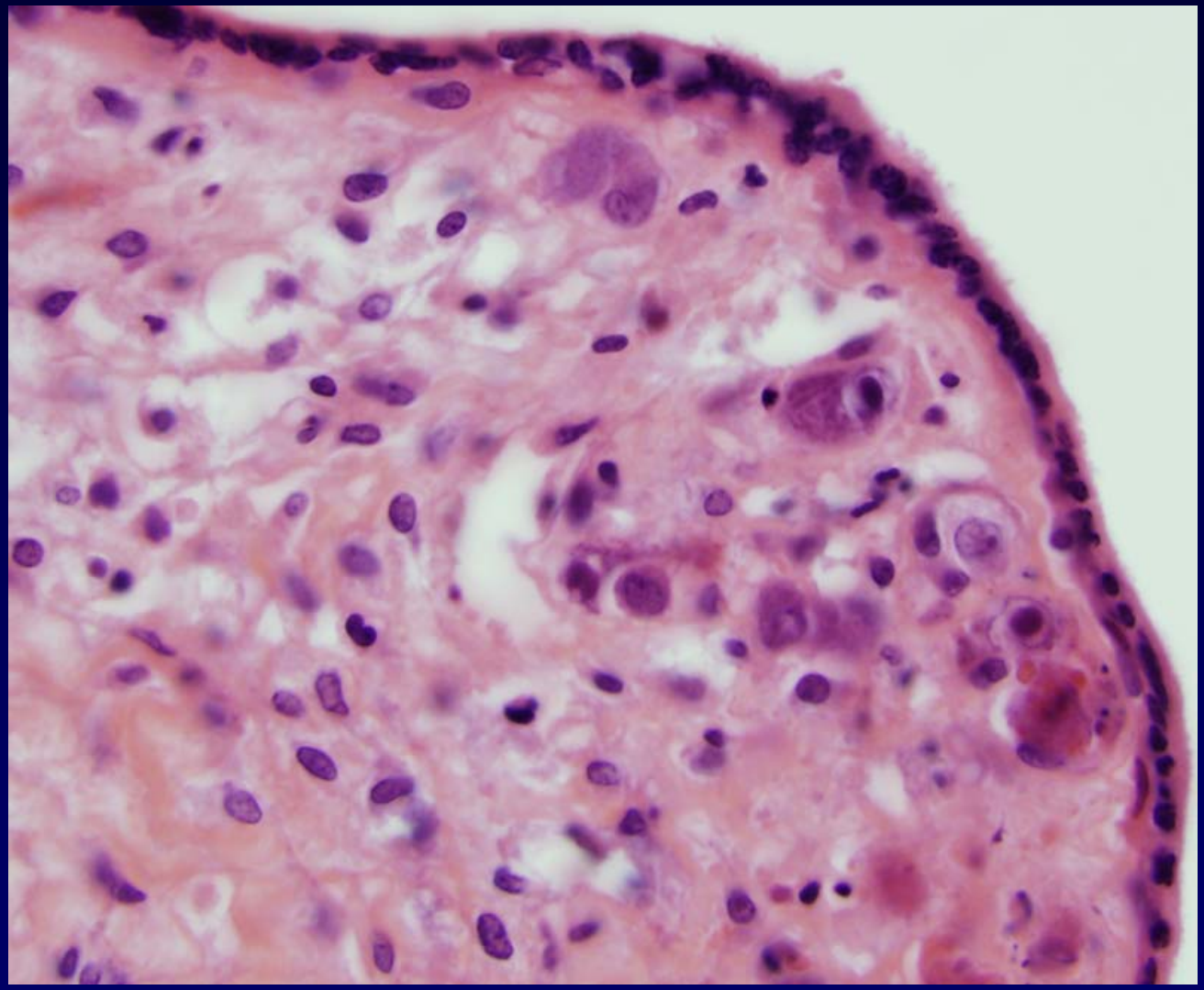
Inclusions in stromal cells

CMV



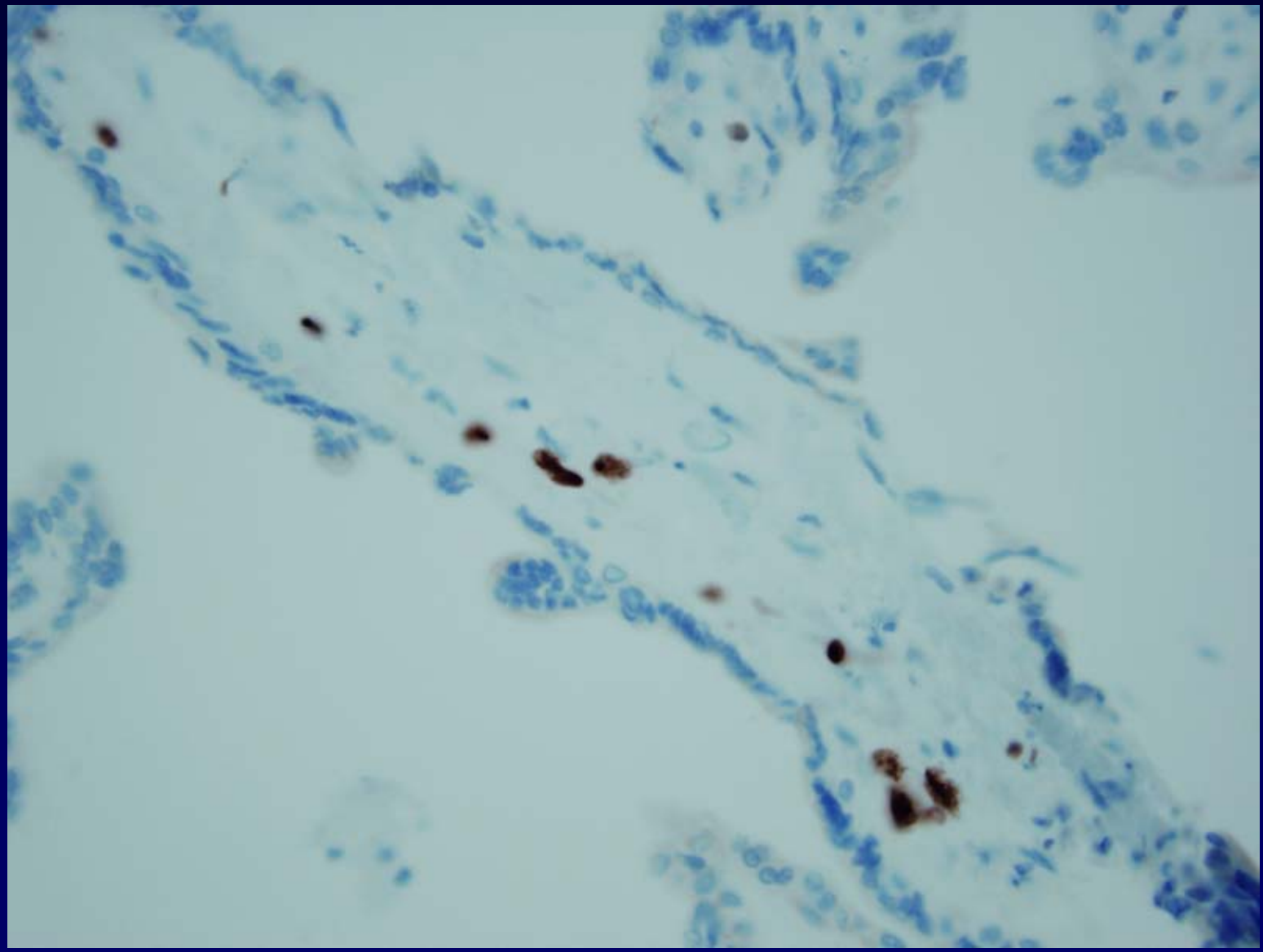
Inclusions in endothelial cells

CMV



Eosinophilic nuclear and basophilic cytoplasmic inclusions

CMV



CMV Placentitis

- Lymphoplasmacytic villitis
- Necrotizing vasculitis
- Vessel occlusion
- Stromal hemosiderin
- Viral inclusions – 20%

CMV Placentitis

Immunohistochemistry, in situ hybridization and PCR will detect CMV in cases of congential infection

- When placenta is normal
- When infection is sub clinical

Congenital CMV Infection

- 0.2% to 2.5% of live births
  - 5 to 10% have disseminated disease
  - 90% unrecognized at birth
    - 5% to 15% have long-term effects
      - Mental retardation
      - Learning disabilities
      - Sensorineural hearing loss

Congential CMV Infection

- In utero > intra partum, post partum
- Caused by 1º or 2º infection
- If 1º more likely:
  - Symptomatic
  - Late sequelae
- Treatment immediately after birth may decrease severity of neurologic damage

Congenital CMV Infection

- Recent evidence that decidual cells or decidual macrophages are reservoir for CMV
- Reactivation is more likely after inflammatory response to bacterial infections

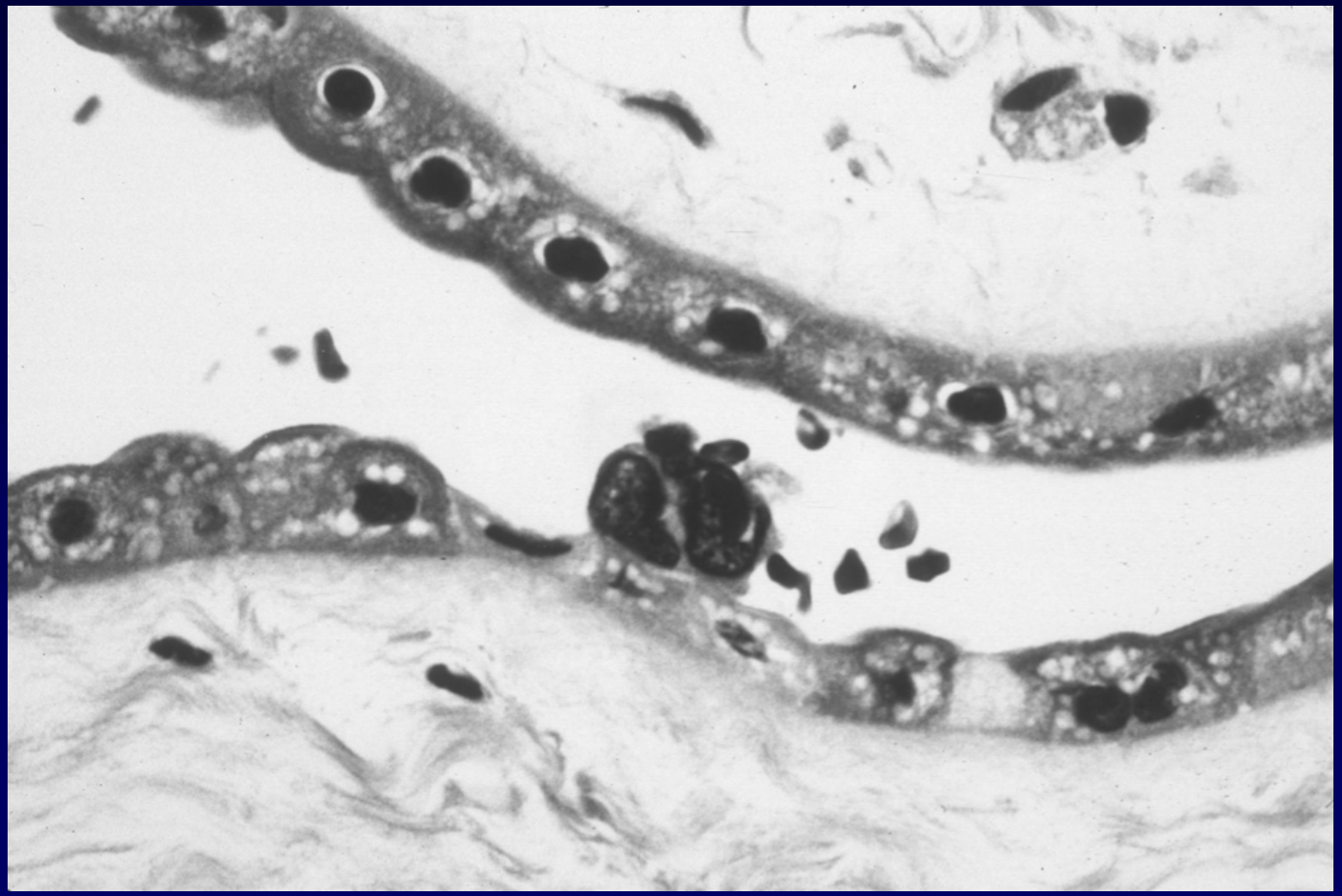
Congenital CMV Infection

- Usually infected women are asymptomatic
- No guidelines for treating CMV during pregnancy
- Role of screening pregnant women for CMV is unclear

Herpes Simplex Virus

- Disseminated HSV infection in newborn is severe and often lethal
- HSV usually acquired during delivery
- Rarely ascending
  - See acute chorioamnionitis,lymphocytes, plasma cells, rarely viral inclusions
  - In situ or immunohistochemistry may be helpful

Herpes Simplex Virus



Herpes Simplex Virus

- Hematogenous infection is rare
  - Necrotizing lymphocytic villitis
- Syncytiotrophoblast show decreased expression of 3 HSV entry mediators
  - Effectively prevents most HSV from entering fetal circulation

Parvovirus B19

Small, single-stranded DNA virus

- Children - erythema infectiosum
- Adults - asymptomatic
- Pregnant - flu-like illness, polyarthralgia
- Sickle cell - aplastic crisis

Parvovirus B19

- 50% of pregnant women are immune
- ~ 20% of exposed non-immune women will be infected
  - Most fetuses are unaffected
  - Fetal death ~ 9%
    - Infection occurs before 20 weeks
    - Fetus dies between 20 and 28 weeks

Parvovirus B19

Virus infects

- Erythrocyte precursors
- Cardiac myocytes
- Endothelial cells

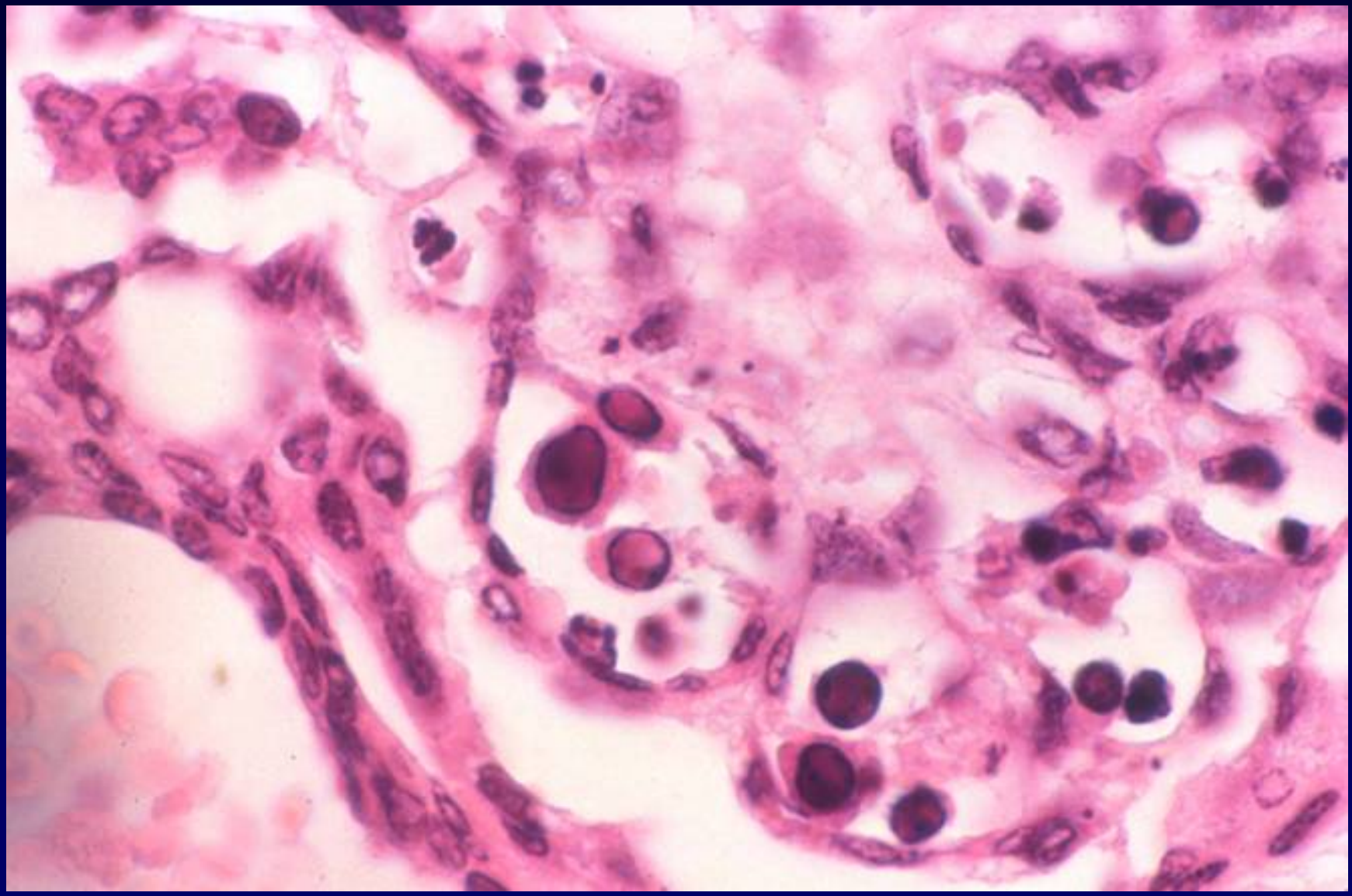
Causes fetal anemia, heart failure, hydrops fetalis

Parvovirus B19

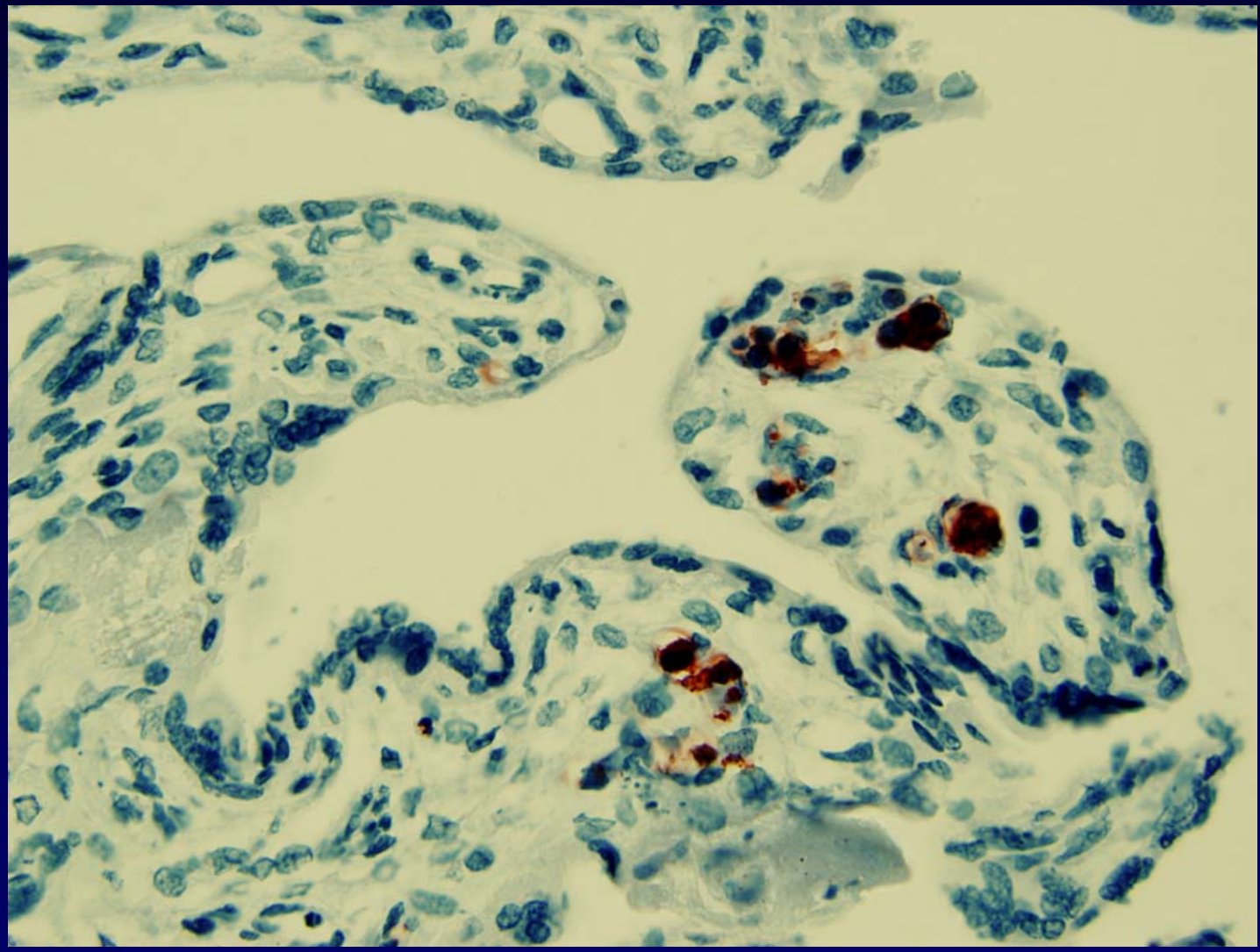
Placental findings

- Often large and pale
- Edematous villi, increased nucleated RBCs
- No villitis
- Eosinophilic intranuclear inclusions
  - Red cell precursors
- Immunohistochemistry, in situ, PCR may help
  - PCR difficult to interpret – maternal blood is viremic

Parvovirus



Parvovirus



Immunostain for parvovirus

Human Immunodeficiency Virus

- Mechanisms of mother to child transmission
  - In utero - transplacental
  - During delivery - most common
  - Postnatal - breast feeding

Human Immunodeficiency Virus

- Role of placenta in promoting or preventing HIV passage is not well understood
  - By IHC, in situ, PCR can find HIV antigens/DNA
    - Trophoblast, Hofbauer cells, villous endothelium, amnion
    - Does not correlate with infant viral culture or infant infection

Human Immunodeficiency Virus

Placental findings

- No consistent pattern
  - In one large study placentas from HIV +
    - Chorioamnionitis – more likely
    - Plasma cell deciduitis – more likely
    - Villitis – less likely
  - Transmission rate – related to chorioamnionitis in some studies but not others

Human Immunodeficiency Virus

Co infection with malaria

- Very common in areas of Africa
- ↑ severity of malaria infection in pregnant women
- ↑ rate of mother to child transmission of HIV
- ↑ rate of preterm delivery, low birth weight, infant mortality

Syphilis

- Resurgence in 1980’s with decline by late 1990’s
- Serologic diagnosis in neonate is difficult
- CDC requirements for diagnosis - find spirochetes in
  - Fetal/neonatal tissue
  - Placenta or cord

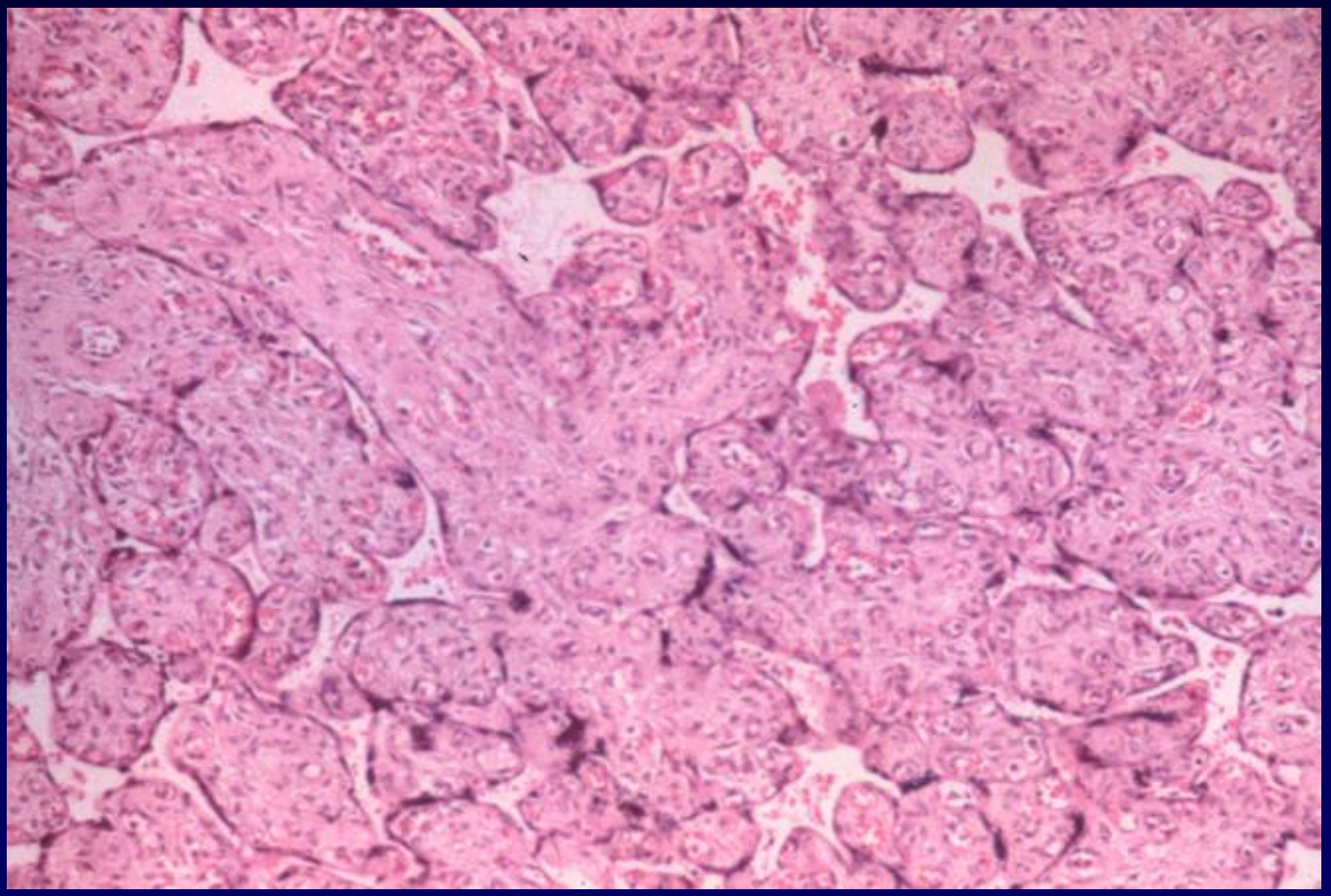
Syphilis

- Gross
  - Large, bulky placenta
  - Normal
- Micro - classic triad
  - Large, hypercellular, immature villi
  - Proliferative fetal vascular changes
  - Villitis - chronic or active

Syphilis

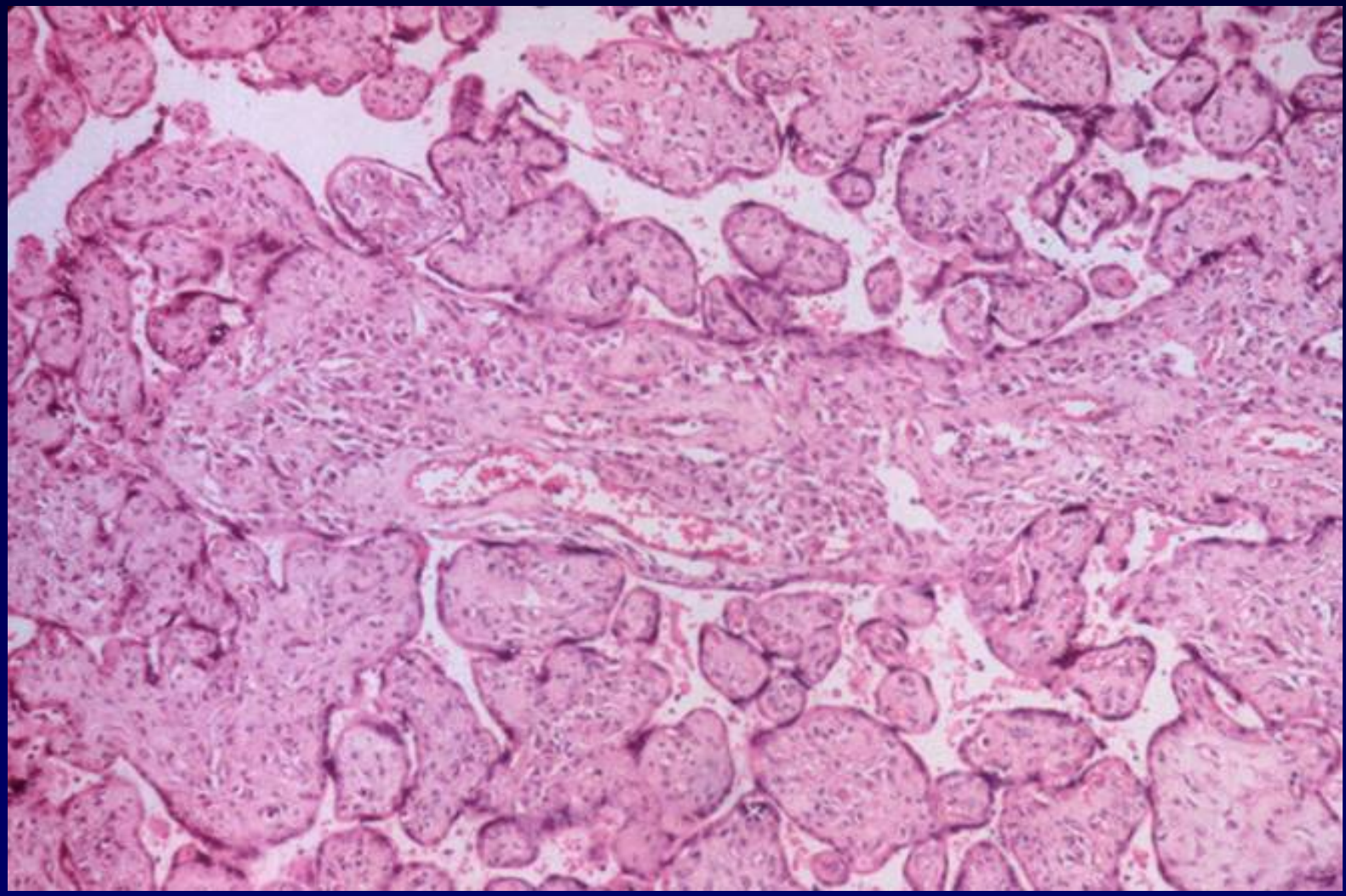
- Classic triad – 43%
- Two of three – 47%
- One feature – 10%
- Other helpful features:
  - Intra or perivillous polys
  - Lymphoplasmacytic deciduitis
  - Necrotizing funisitis

Syphilis



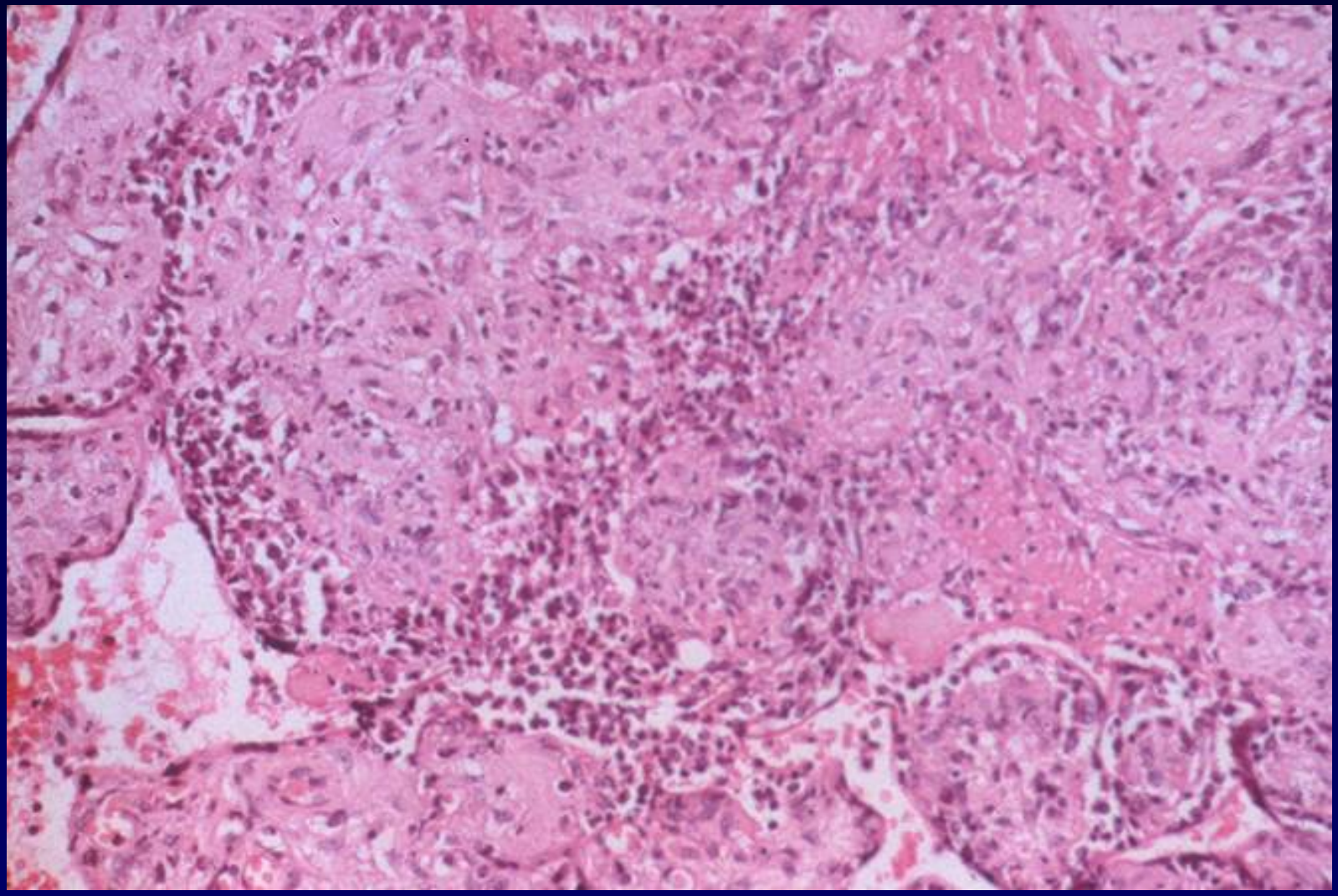
Large, edematous villi

Syphilis



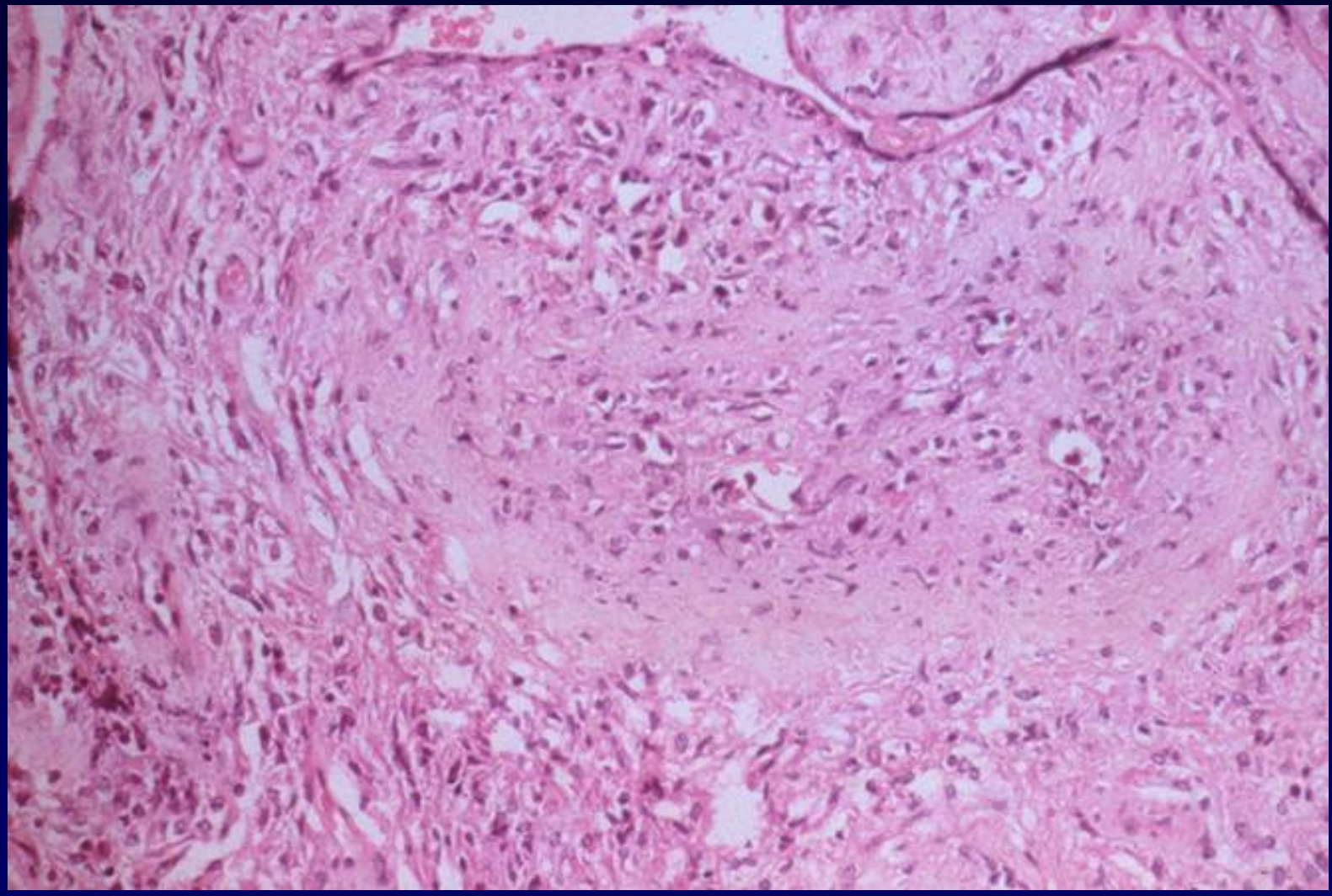
Proliferative vascular changes

Syphilis



Destructive villitis with polys

Syphilis



Proliferative vascular changes

Syphilis

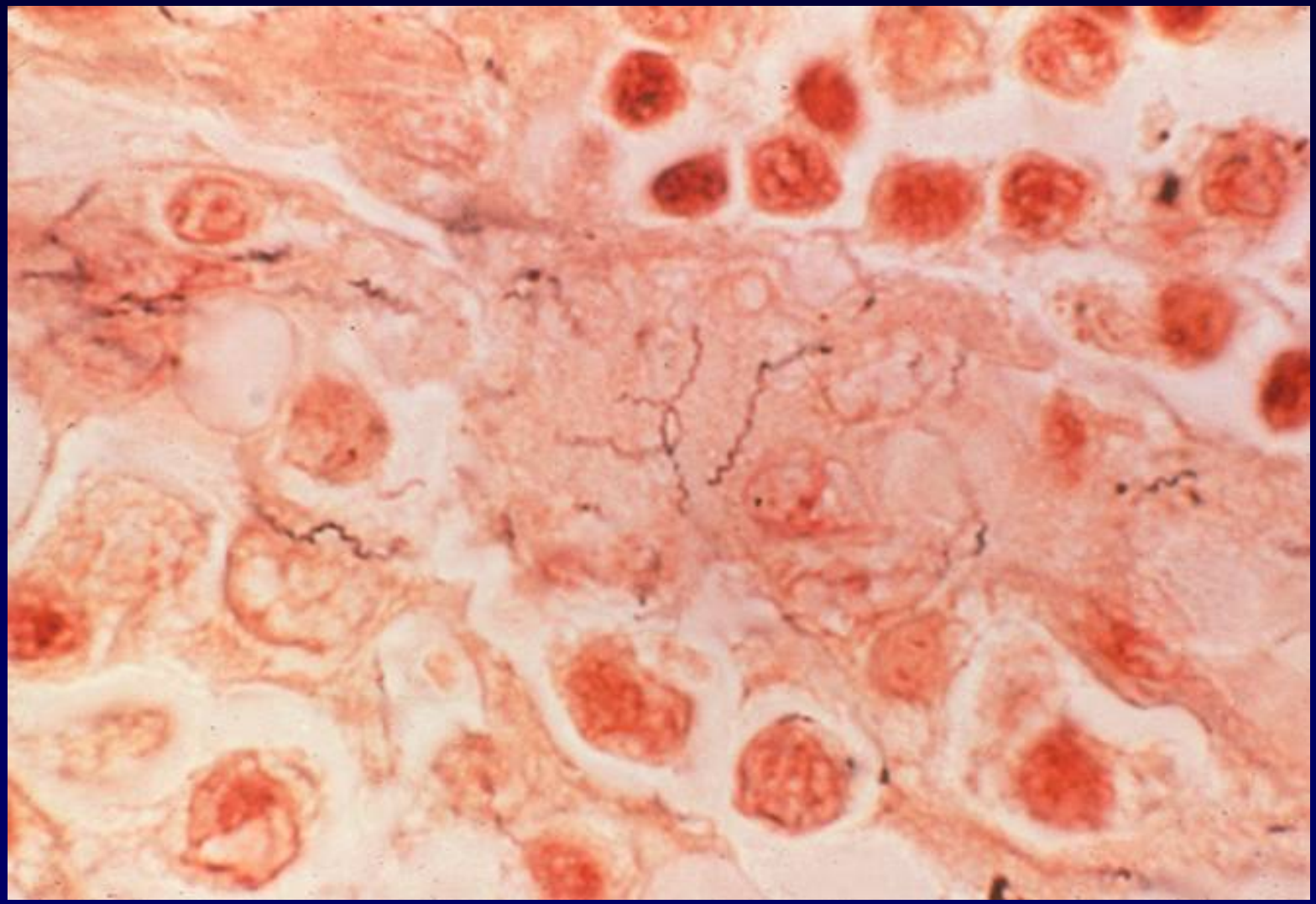
- Strong association between classic triad and
  - Spirochetes on silver stain
  - *Treponema pallidum* DNA on PCR
- PCR may identify DNA when staining is negative
- Number of organisms in tissue is low

Syphilis

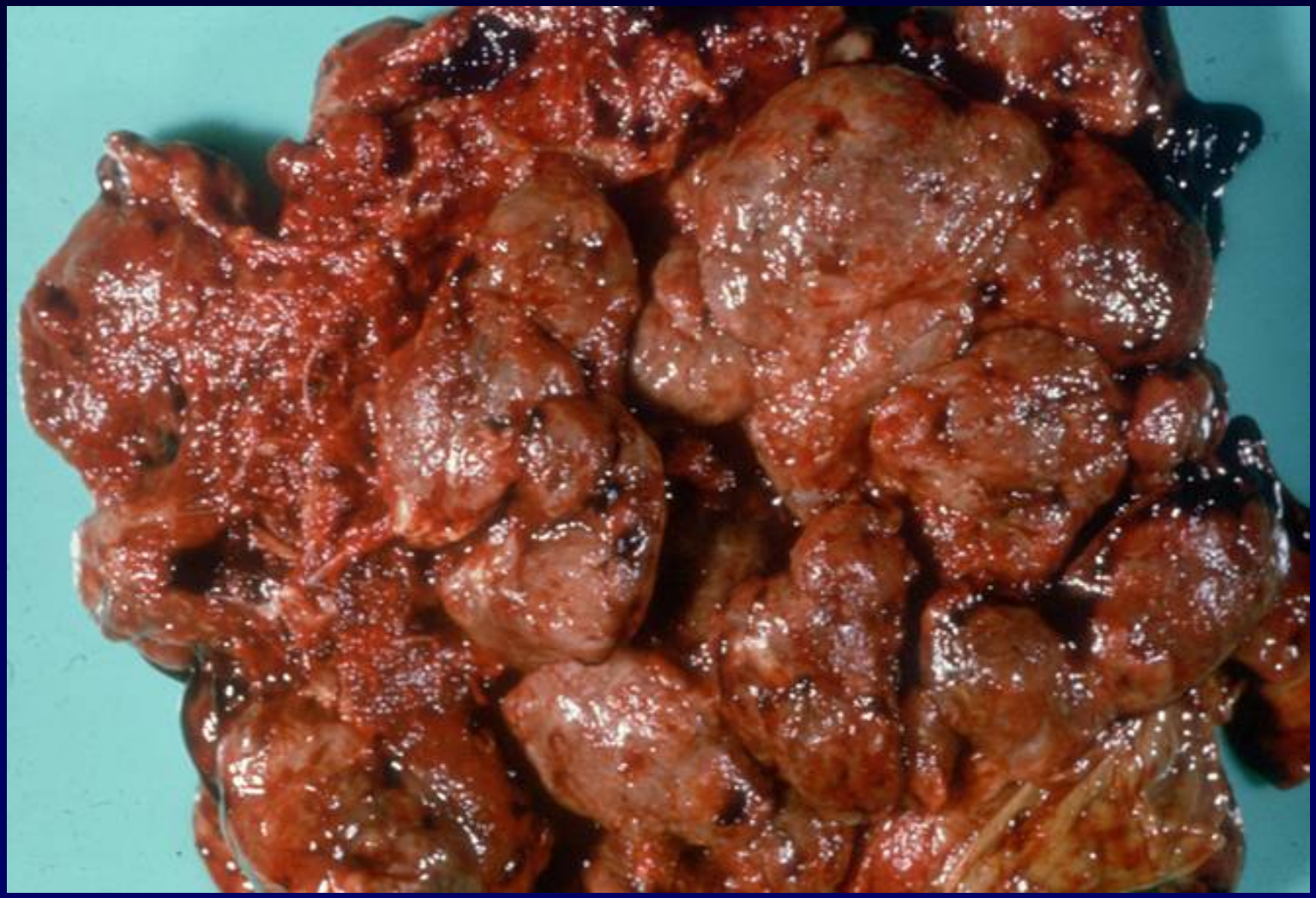
Best places to find spirochetes

- Cord
- Free membranes
- Decidua
- Sclerotic villi adjacent to villitis

Syphilis

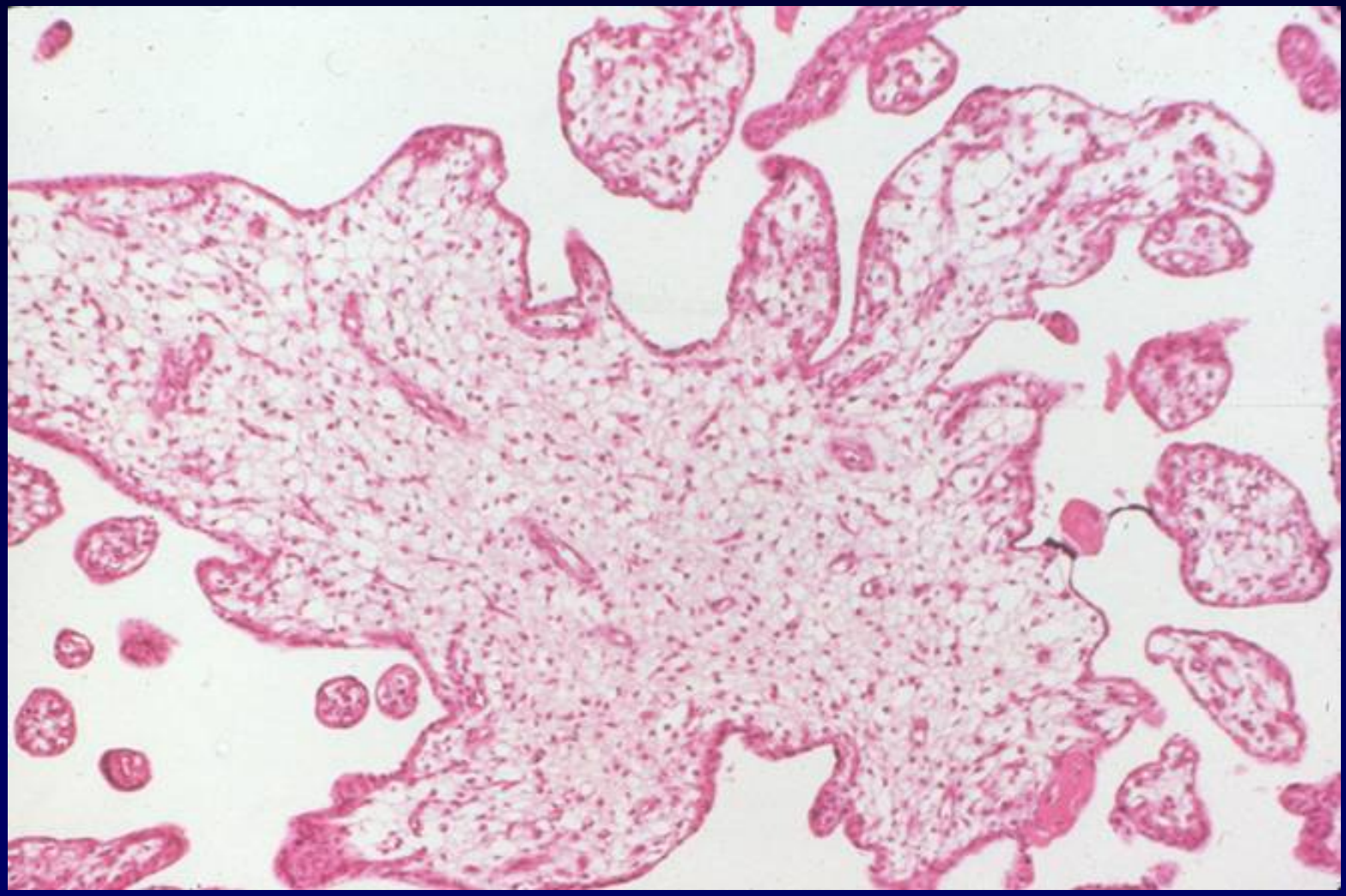


Toxoplasma Gondii



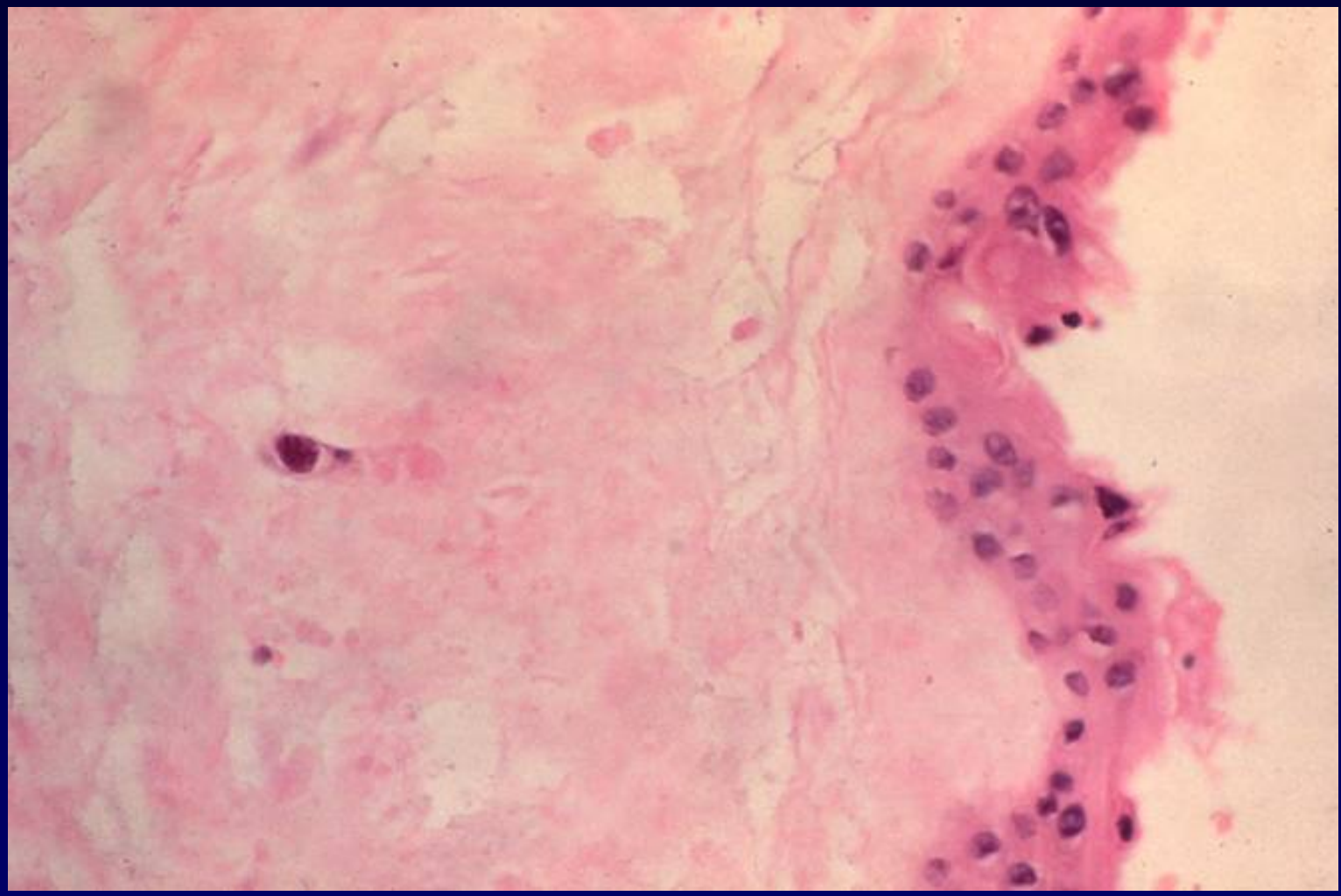
Often big, bulky placenta

Toxoplasmosis



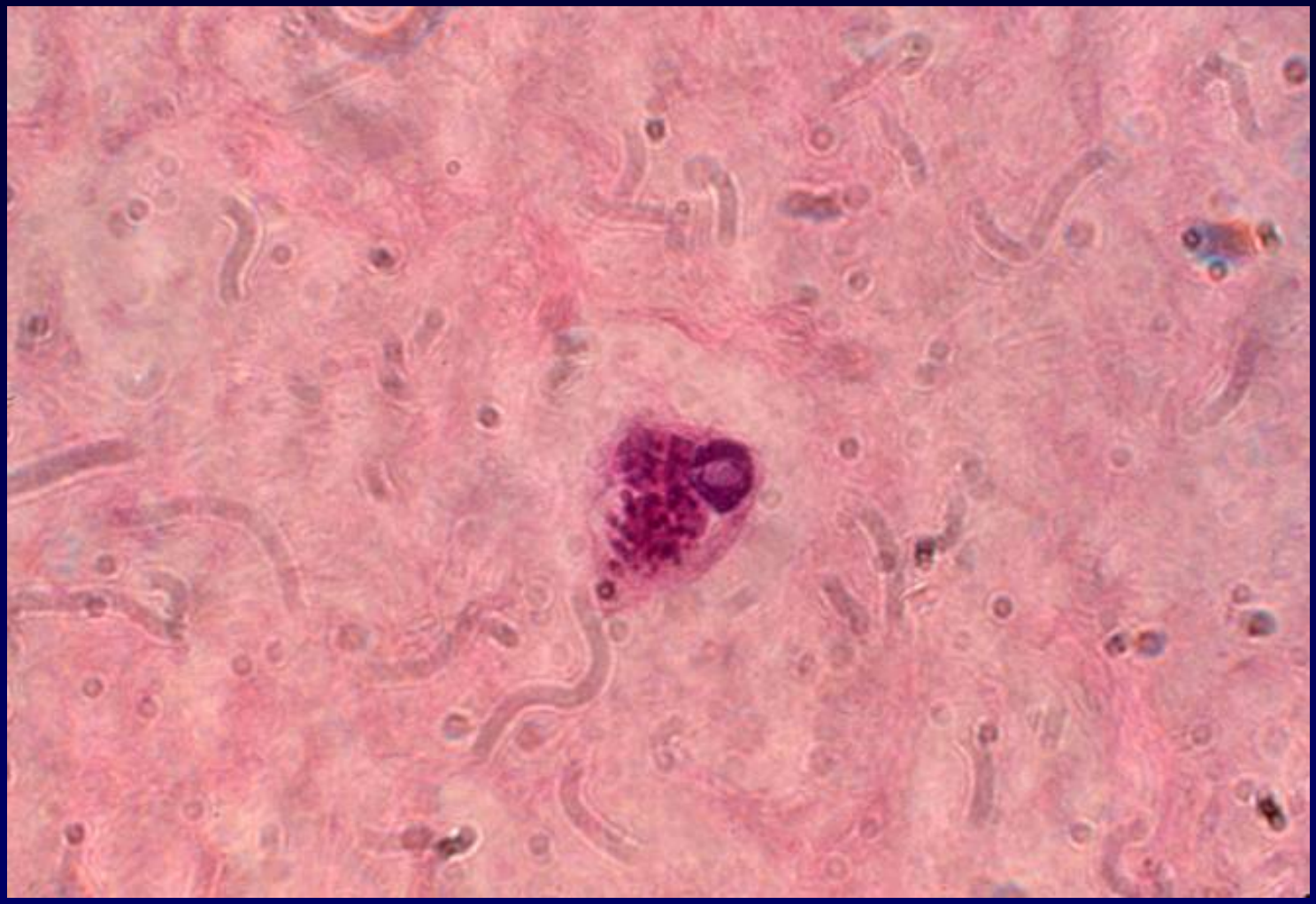
Immature villi with subtle villitis

Toxoplasmosis



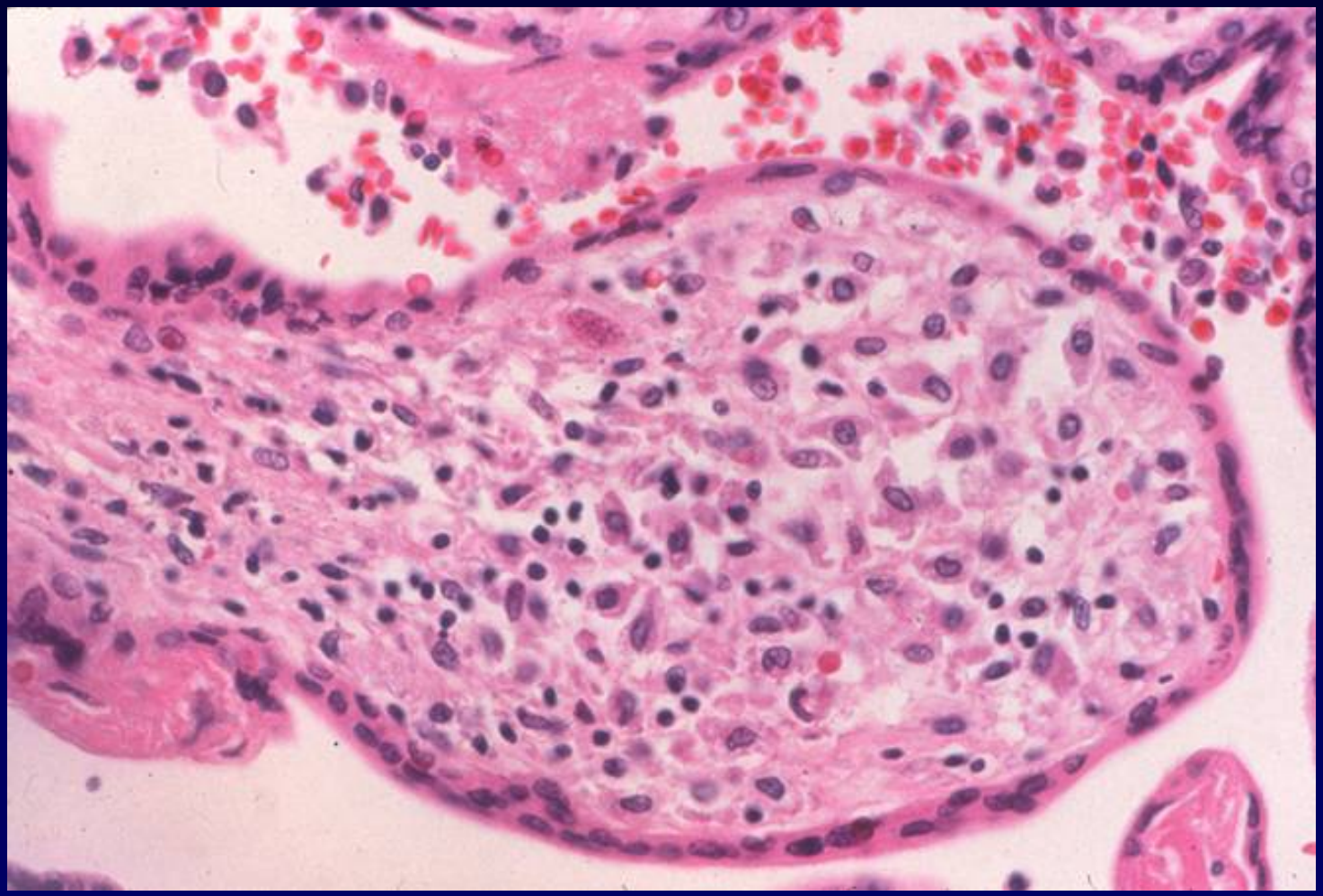
Cyst with no surrounding inflammation

Toxoplasmosis



Cyst with tachyzoites inside

Toxoplasmosis



Lymphocytic villitis in response to tachyzoites

Toxoplasmosis

Placental findings

- Villitis
  - Usually subtle, non-necrotizing
  - May be extensive with fibrosis or granulomas
- Plasma cell deciduitis
- Increased nucleated RBCs
- Chronic chorioamnionitis, funisitis
- Thrombosis, calcification of chorionic plate vessels

Toxoplasmosis

Cysts can be found in

- Cord
- Membranes
- Villi
- Decidua

Immunohistochemistry, immunofluorescence and PCR may be helpful

Congenital Toxoplasmosis

- Almost always after primary infection
  - Reactivation is rare
- In US only one-third of woman are immune
- Maternal infection occurs from ingesting
  - Oocysts in cat feces, unwashed vegetables, soil (gardening)
  - Tissue cysts in undercooked meat

Congenital Toxoplasmosis

After maternal primary infection

- 35% to 50% of fetuses are infected

Maternal infection late in gestation

- ↑ risk of fetal infection

Maternal infection early in gestation

- ↑ severity of sequelae

Congenital Toxoplasmosis

Congenitally infected infants

- Usually asymptomatic at birth
- Most develop sequelae such as:
  - Blindness
  - Deafness
  - Microcephaly
  - ↓ IQ

Congenital Toxoplasmosis

- Treatment as close to maternal infection significantly decreases
  - Number of infants with sequelae
  - Number with severe sequelae
- Optimizing screening programs is important in high infection areas

Villitis of Unknown Etiology

- Accounts for majority of villitis
- Incidence
  - 6% to 26%
  - Usually greater than 32 weeks gestation
- No gross abnormalities
- 85% are very mild or mild
- Most randomly distributed
  - 20% have basal location

Villitis of Unknown Etiology

- Most cases are necrotizing
- Most are lymphohistiocytic
- May be associated with vasculitis of fetal stem vessels
  - Avascular downstream terminal villi

Villitis of Unknown Etiology

Theories of pathogenesis

- Result of unidentified pathogen
- Immunologic phenomenon

Villitis of Unknown Etiology

- Inflammatory cells
  - Maternal
  - T helper cells
  - Ia antigen-bearing macrophages
- ↑ incidence in women with autoimmune disorders
- Tendency to recur

Villitis of Unknown Etiology

Clinical associations

Severity of clinical findings generally related to severity of villitis

- Small for gestational age infants
- Antenatal growth arrest
- Perinatal mortality
- Oligohydramnios without membrane rupture
- Chronic monitoring abnormalities

Villitis of Unknown Etiology

Which cases to work up for infection?

- Suspicious maternal history
- Suspicious clinical findings in neonate
- Moderate or severe villitis
- Pattern besides lymphohistiocytic

Villitis

Basic work up

- IHC for CMV
- IHC for toxo
- Warthin-Starry for spirochetes
- Gram stain if lots of polys or abscesses

Sample Villitis Comment

Histologic sections show mild, necrotizing lymphohistiocytic villitis. No plasma cells or viral inclusions are seen. In most cases of villitis an etiology cannot be established, however, villitis may be seen in infections spread hematogenously from mother to fetus such as CMV, toxoplasmosis, syphilis and others. Infant and maternal serologies may be helpful if clinically indicated.

Implantation Disorders

- Placenta accreta
- Abnormalities of placental shape
- Extrachorial placentation

Placenta Accreta

Clinical feature

- Abnormally adherent placenta

Pathologic feature

- Absence of decidua between villi and myometrium

Placenta Accreta

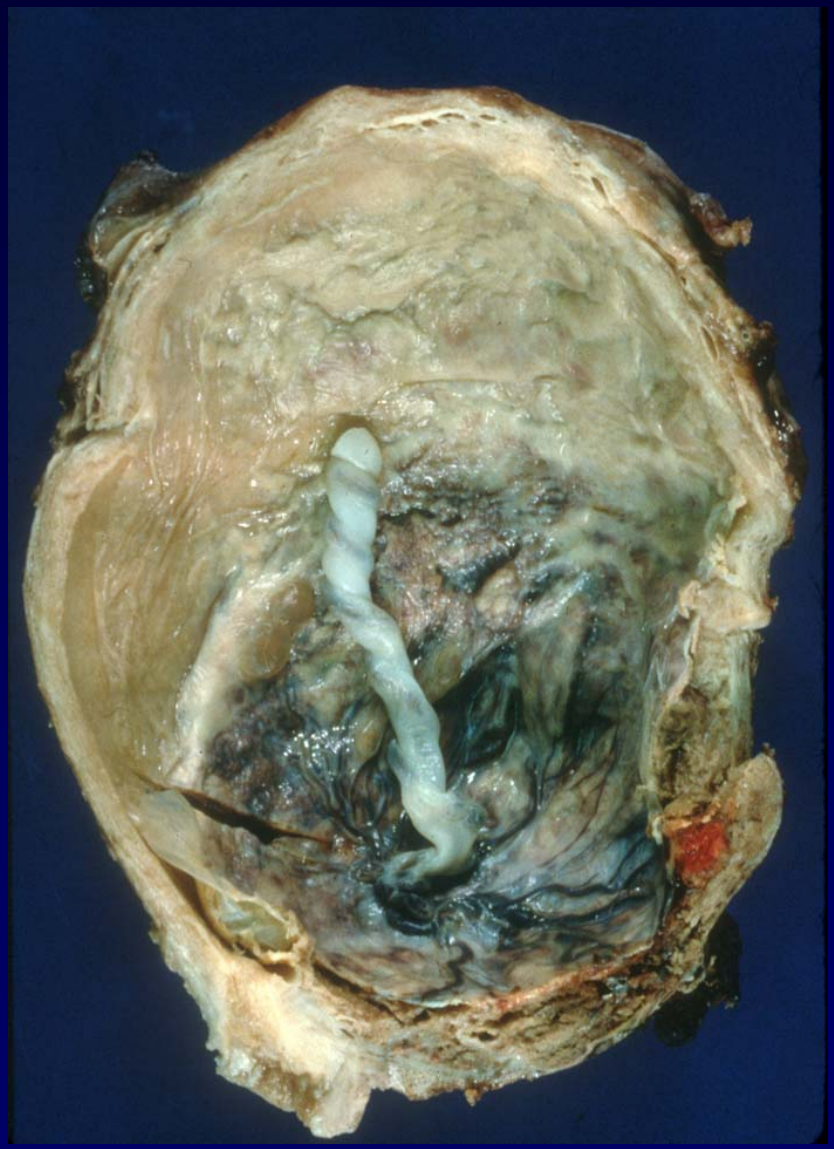
Three categories

- Accreta vera
  - Villi abut but do not invade myometrium
- Increta
  - Villi invade myometrium
- Percreta
  - Villi perforate myometrium

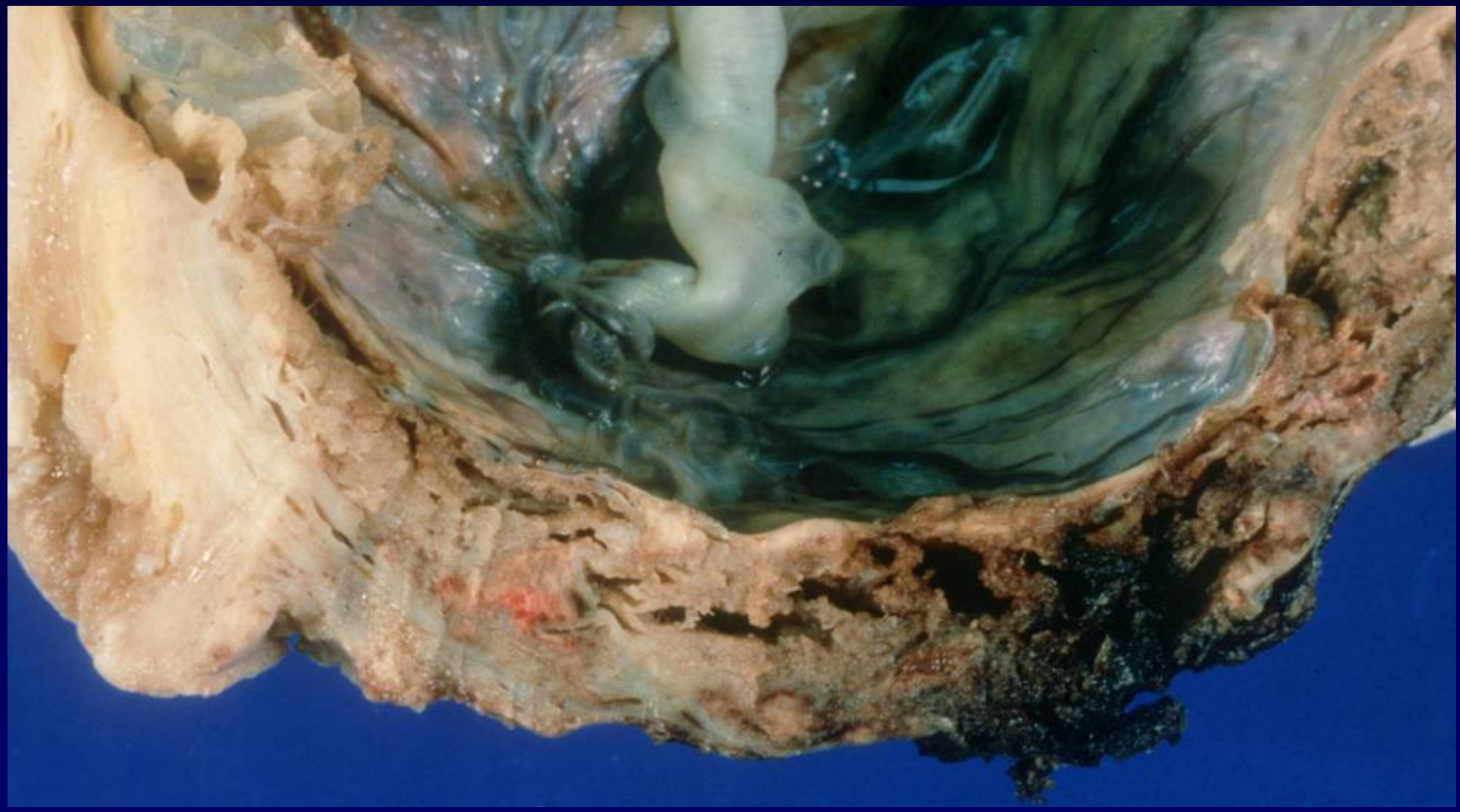
Case 6

The patient is a 35 year old G2P1 woman with placenta previa.

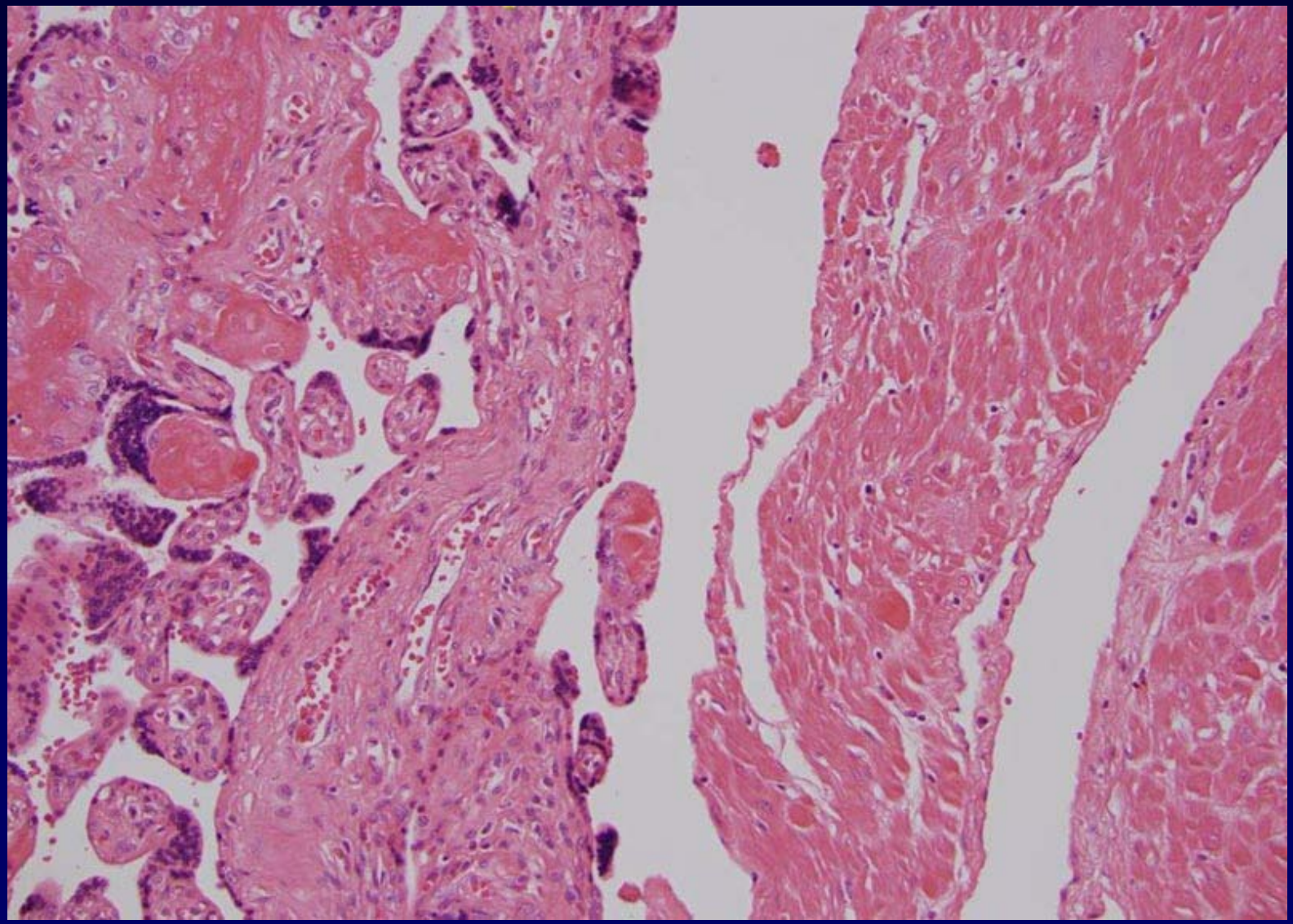
Placenta Percreta



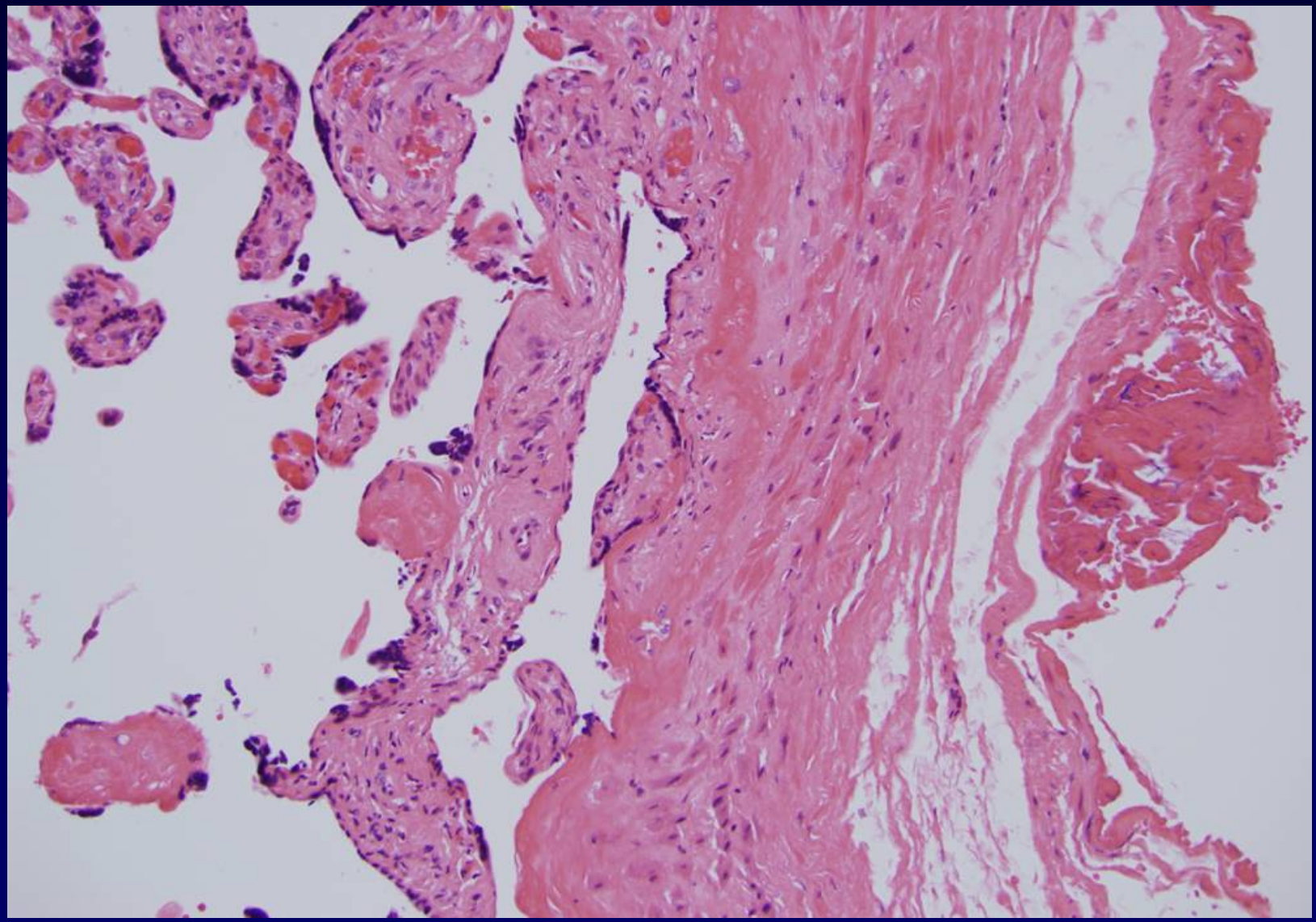
Placenta Percreta



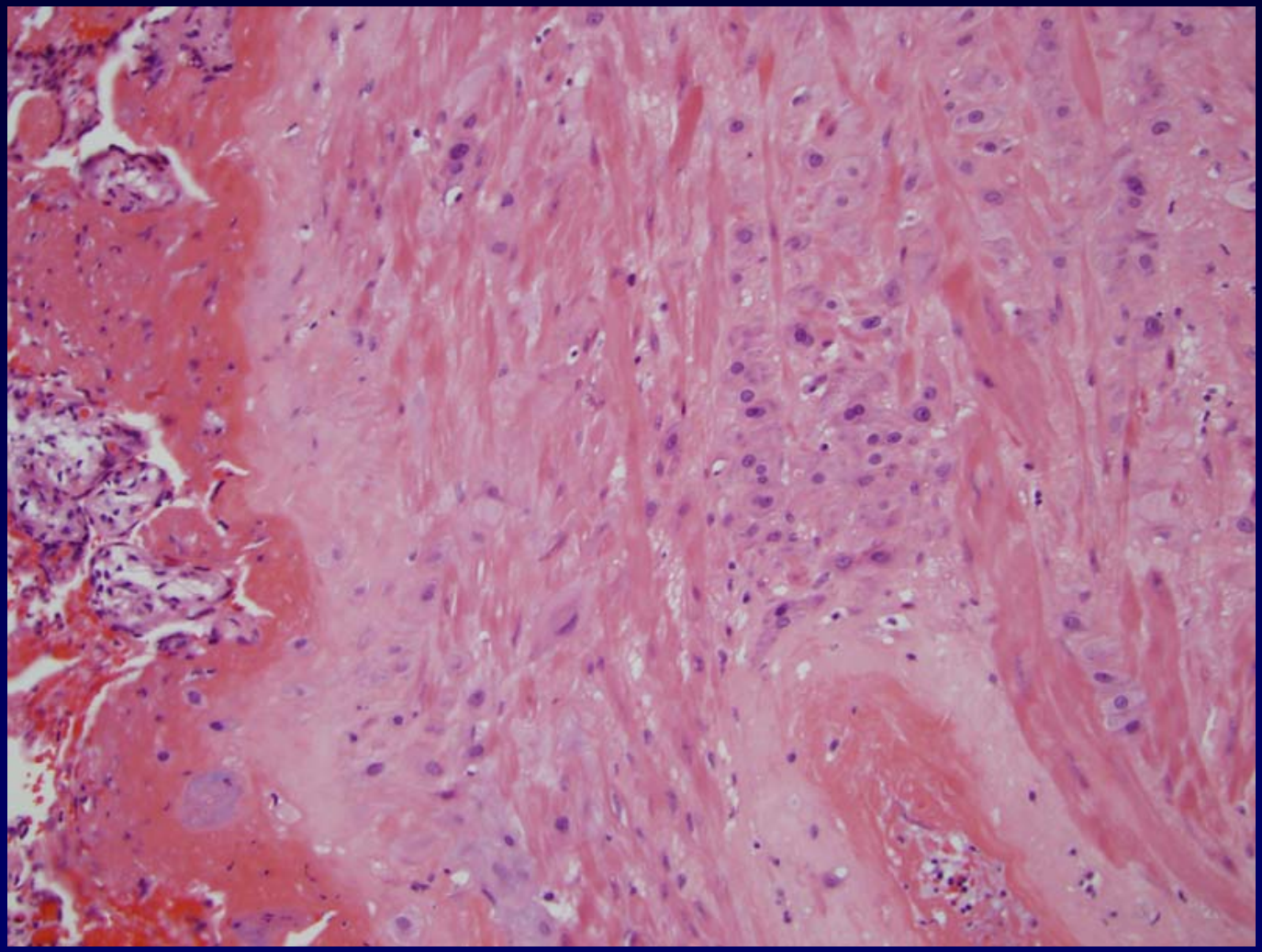
Placenta Percreta



Placenta Percreta

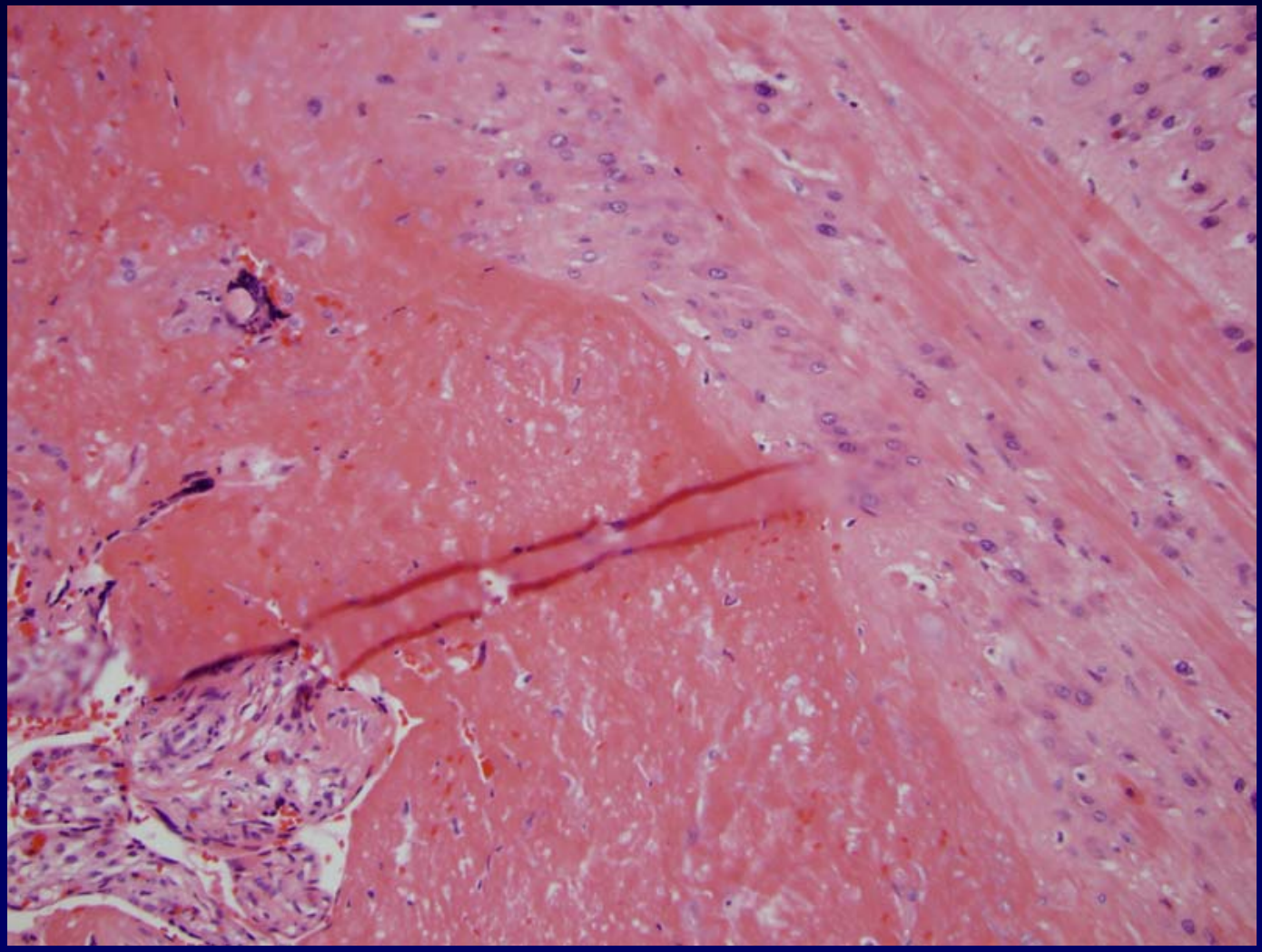


Placenta Accreta



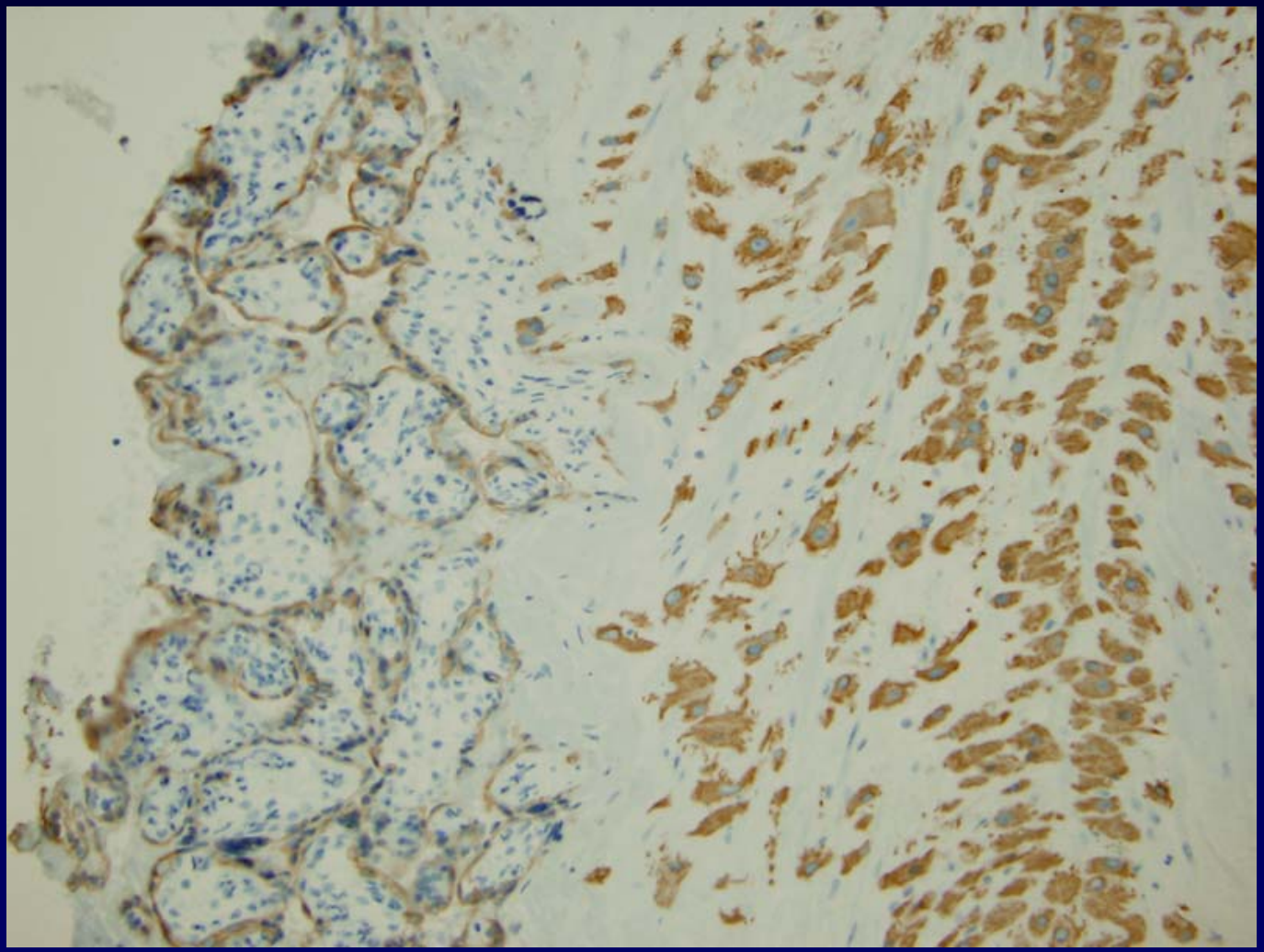
Trophoblast between muscle and villi

Placenta Accreta



Fibrin and trophoblast between muscle and villi

Placenta Accreta



Trophoblast is CK+ but decidua is CK-

Placenta Accreta

Incidence

- 1:540 to 1:93,000
- May reflect partial vs. complete
- Cases confirmed by hysterectomy 1:2500
- 10-fold increase in the last decade

Placenta Accreta

Risk factors

- Major
  - Prior Cesarean section
  - Placenta previa
- Less important
  - Prior D&C, scarring
  - Need for prior manual removal
  - Implantation in cornu, uterine horn
  - Increased maternal age, gravidity, parity

Placenta Accreta

Clinical findings

- Inability to deliver placenta
- Severe postpartum hemorrhage
  - 50% require transfusion
  - May require emergency hysterectomy
- Antepartum bleeding - 30%

Placenta Accreta

Clinical complications

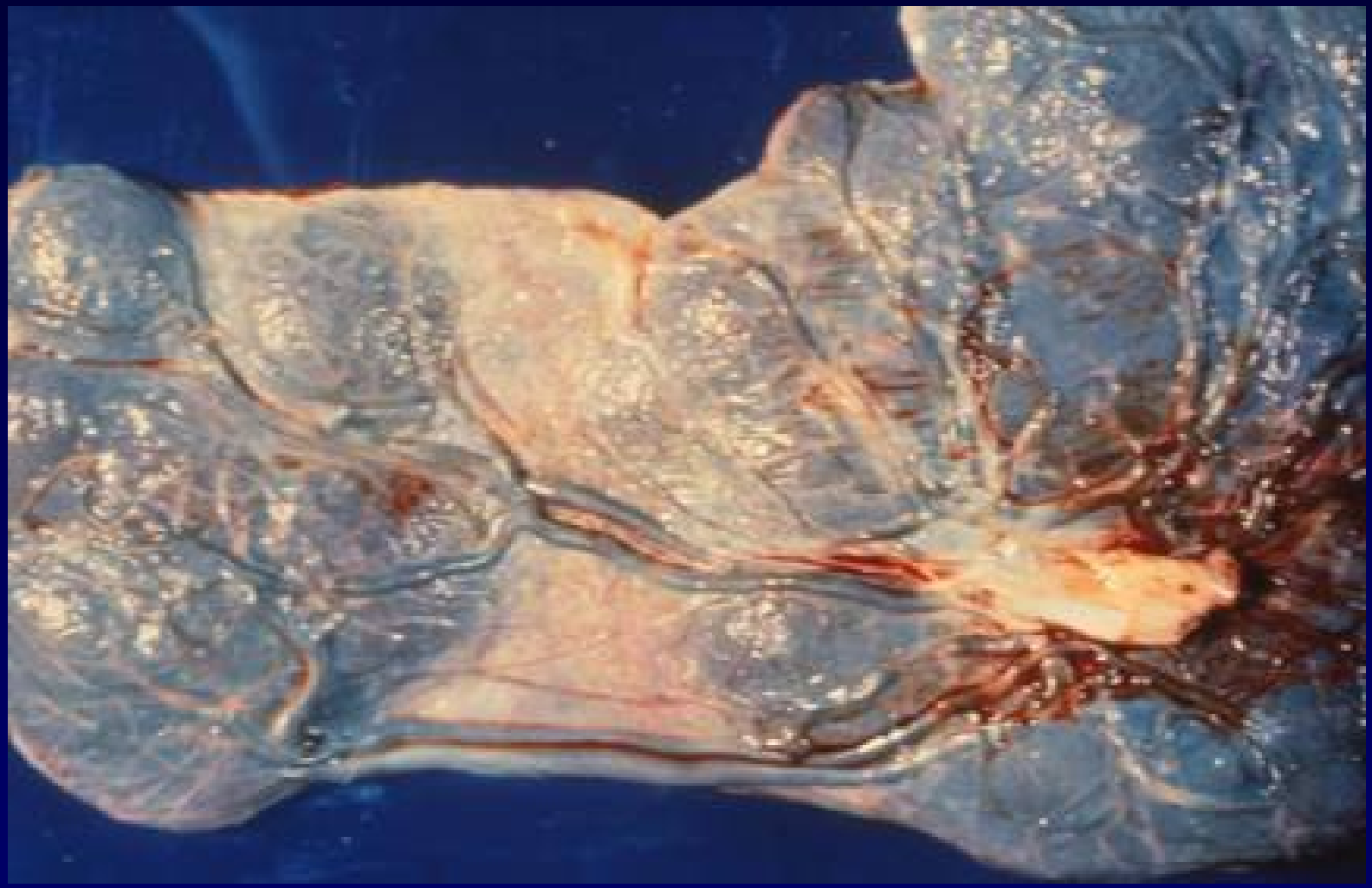
- Uterine rupture - 13.8%
- Uterine inversion - 2%
- Maternal mortality - 7%, from shock, DIC
- Fetal mortality - 1% from uterine rupture, severe antepartum bleeding

Placenta Accreta

Pathogenesis theories

- Implantation in areas of uterus with insufficient decidua
- Early, local hypoxia causes deep trophoblast invasion

Succenturiate Lobe



Succenturiate Lobe

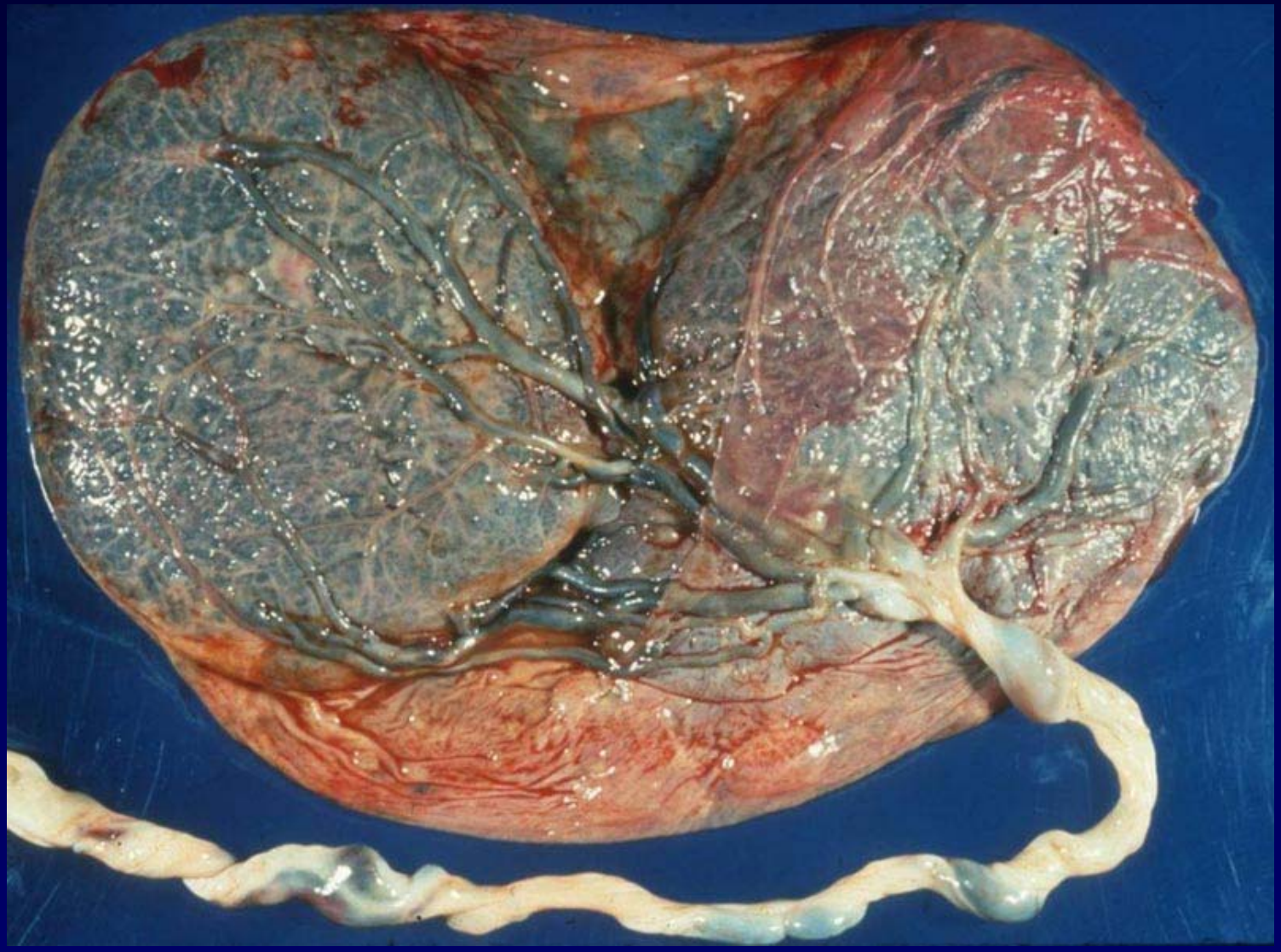
Incidence

- 3% to 5%

Complications

- Retention in uterus – bleeding, infection
- Tear, thrombosis of connecting vessels
- Placenta previa

Bilobed Placenta

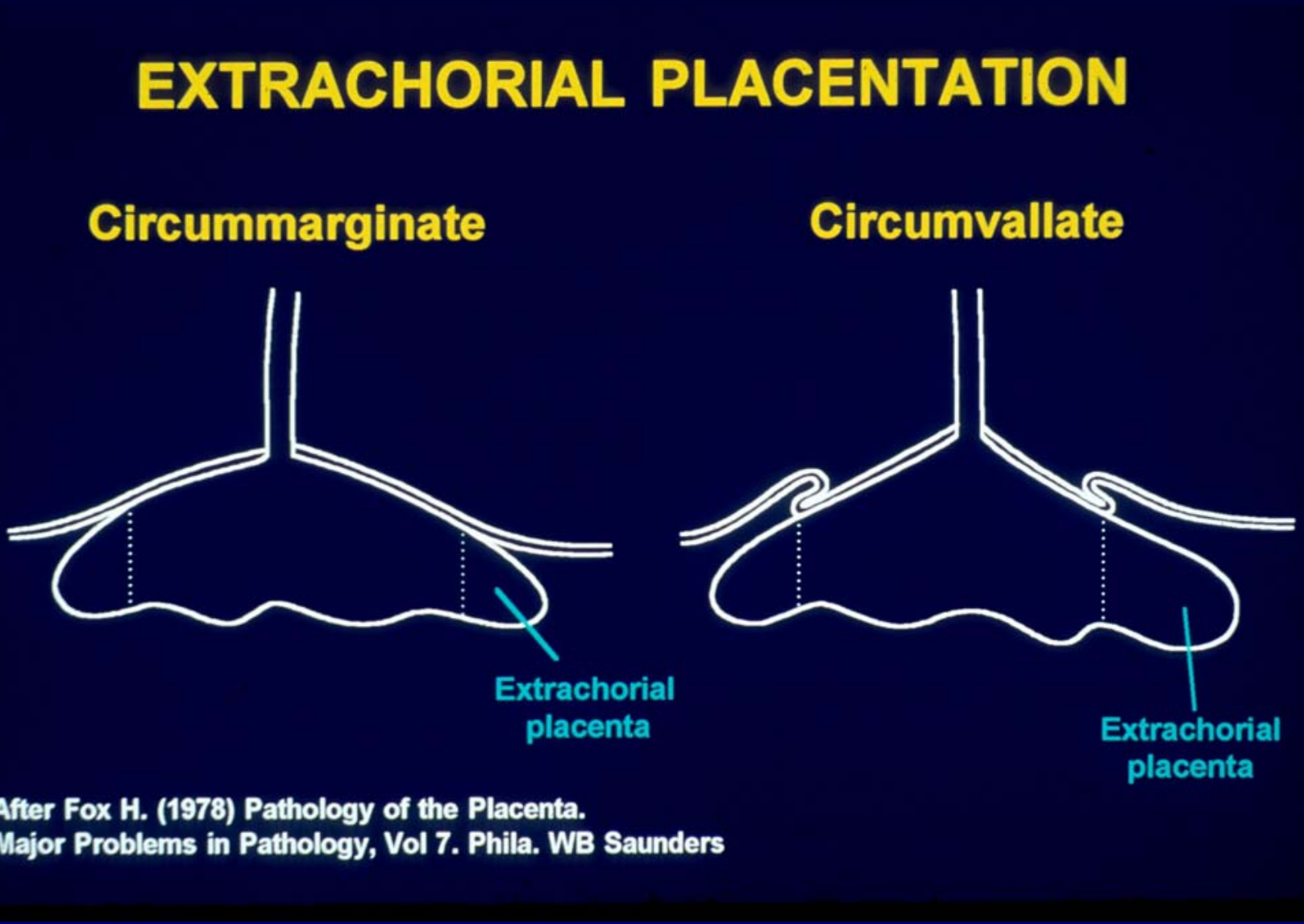


Bilobed Placenta

Clinical associations

- Multiparity
- Advanced maternal age
- History of infertility
- First trimester bleeding
- Need for manual extraction
- No increased fetal or maternal morbidity or mortality

EXTRACHORIAL PLACENTATION

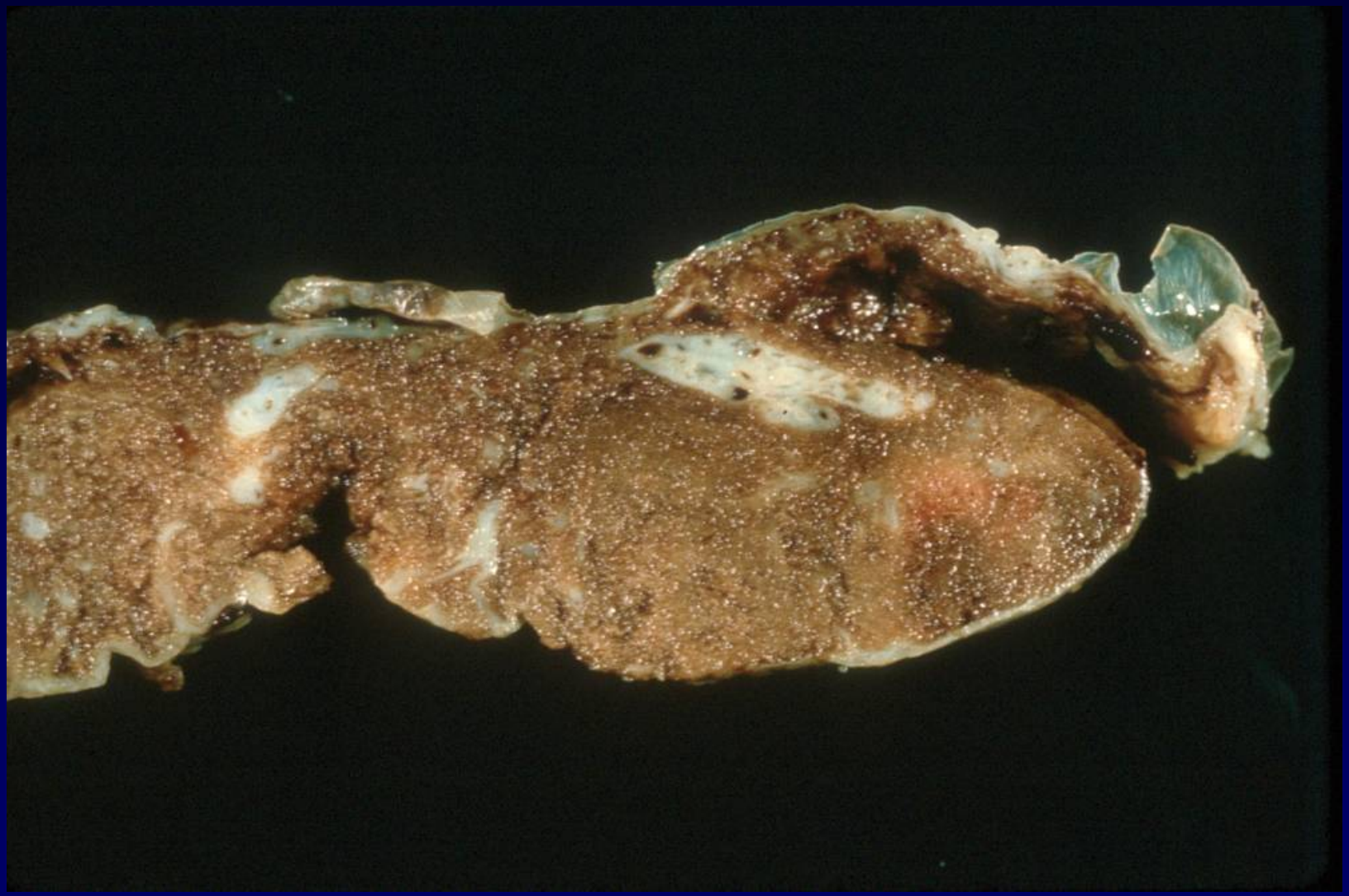


After Fox H. (1978) Pathology of the Placenta.
Major Problems in Pathology, Vol 7. Phila. WB Saunders

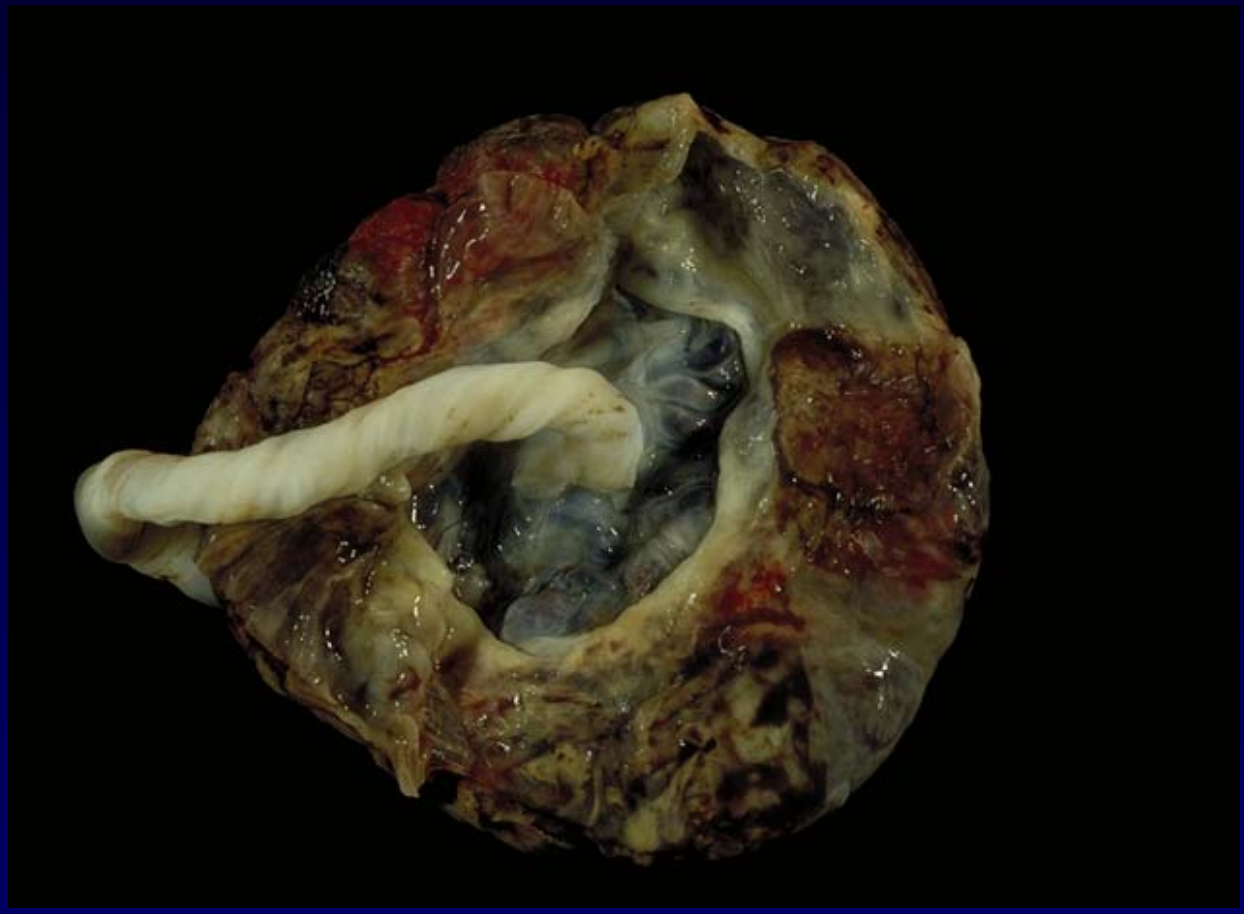
Circummarginate Placentation

- Junction with disc is smooth
- Not clinically significant

Extrachorial Placentation



Circumvallate Placentation



- Junction with disc is thick, rolled
- Preterm bleeding, poor outcome

Extrachorial Placentation

- May be partial or complete
- May have some circummarginate areas and some circumvallate areas in same placenta

Extrachorial Placentation

- Partial circummarginate 13.7%
- Complete circummarginate 3.8%
- Partial circumvallate 4.5%
- Complete circumvallate 2.4%

Extrachorial Placentation

Clinical associations:

- All types increased with increased parity
- Circummarginate
  - Not clinically significant
- Complete circumvallate
  - Recurrent antepartum bleeding
  - Preterm labor and delivery
  - Fetal hypoxia
  - Post partum hemorrhage
  - Recurrence in subsequent pregnancies

Multiple Gestation

- 1 in 90 pregnancies (twins)
- Marked ↑ secondary to assisted reproductive technologies
  - 50% of twins conceived through ART
  - Dramatic ↑ triplets, higher order multiples
    - 75% due to ART
- All twins have ↑ mortality and ↑complications compared to singletons

Twin Gestations

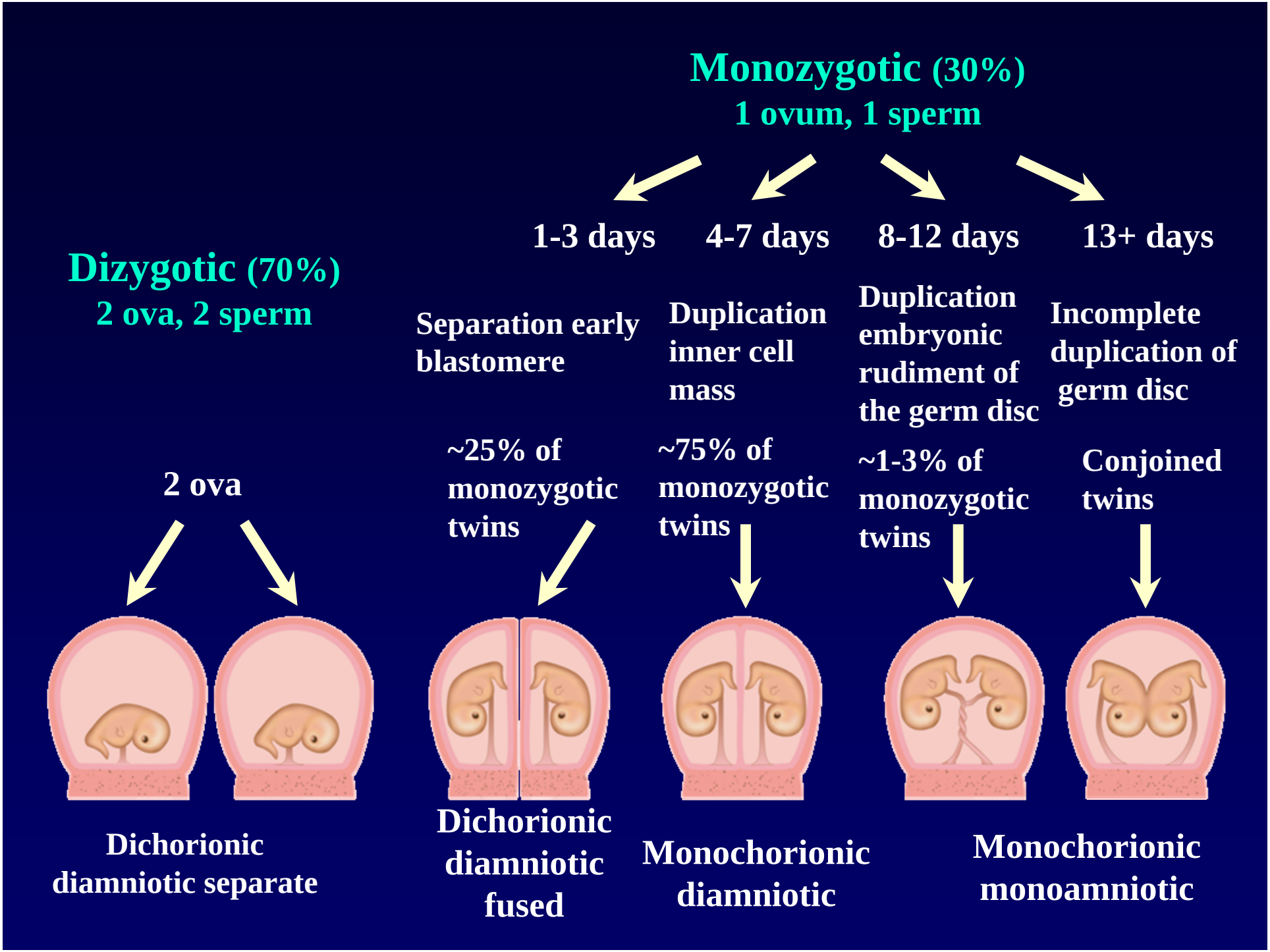
Dizygous (fraternal)

- Account for 70% of twins
- Fertilization of two ova
- Rates vary with population
  - Genetic tendency to poly ovulation
- Dichorionic placentation

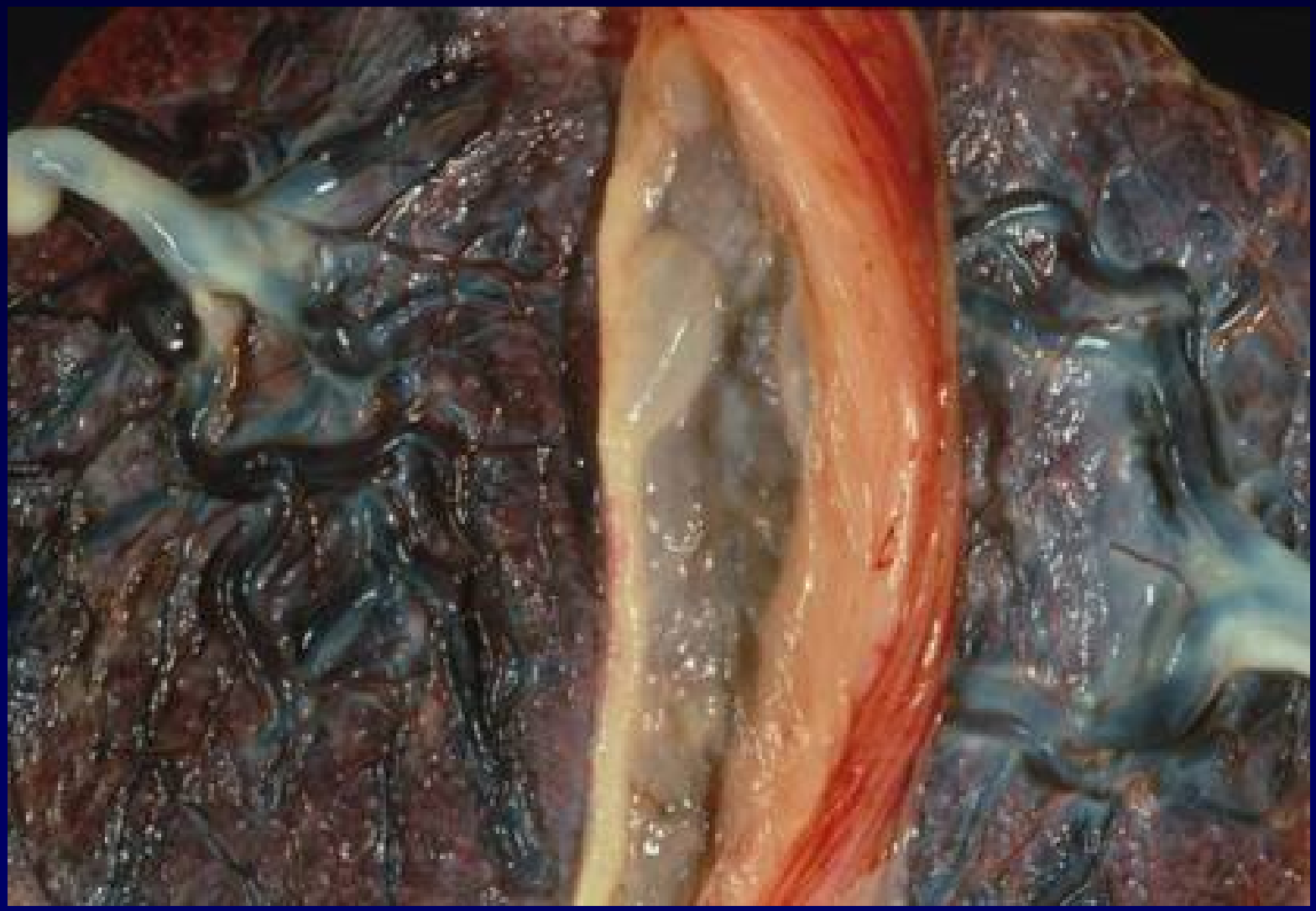
Twin Gestation

Monozygous (identical)

- Account for 30% of twins
- Fertilization of one ovum with post fertilization splitting
- Rate is constant
- Any type of placentation
  - depends on timing of split

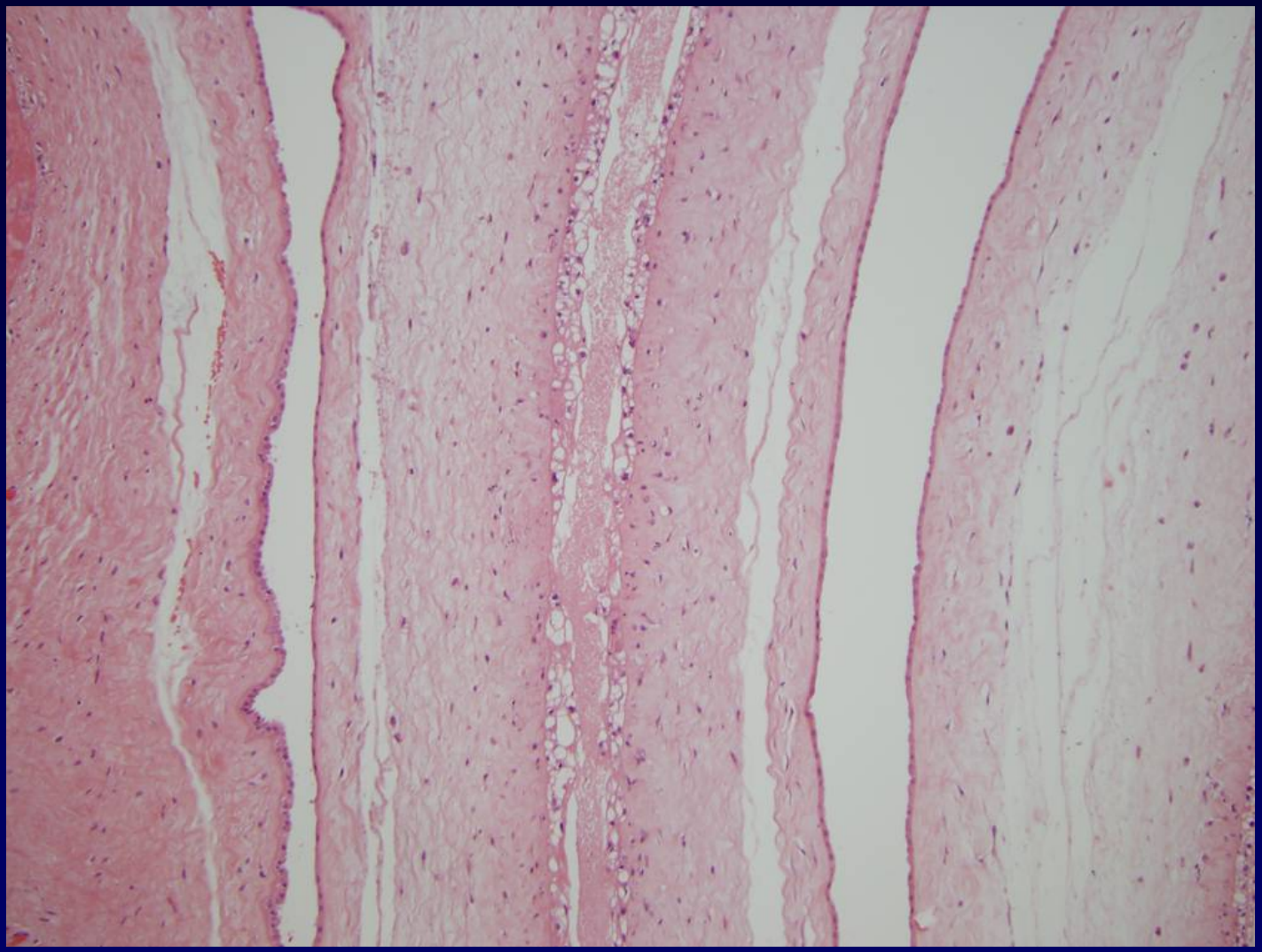

Monozygotic (30%)
1 ovum, 1 sperm
1-3 days
4-7 days
8-12 days
13+ days
Dizygotic (70%)
2 ova, 2 sperm
Separation early blastomere
Duplication inner cell mass
Duplication embryonic rudiment of the germ disc
Incomplete duplication of germ disc
2 ova
~25% of monozygotic twins
~75% of monozygotic twins
~1-3% of monozygotic twins
Conjoined twins
Dichorionic diamniotic separate
Dichorionic diamniotic fused
Monochorionic diamniotic
Monochorionic monoamniotic

Dichorionic Placentation



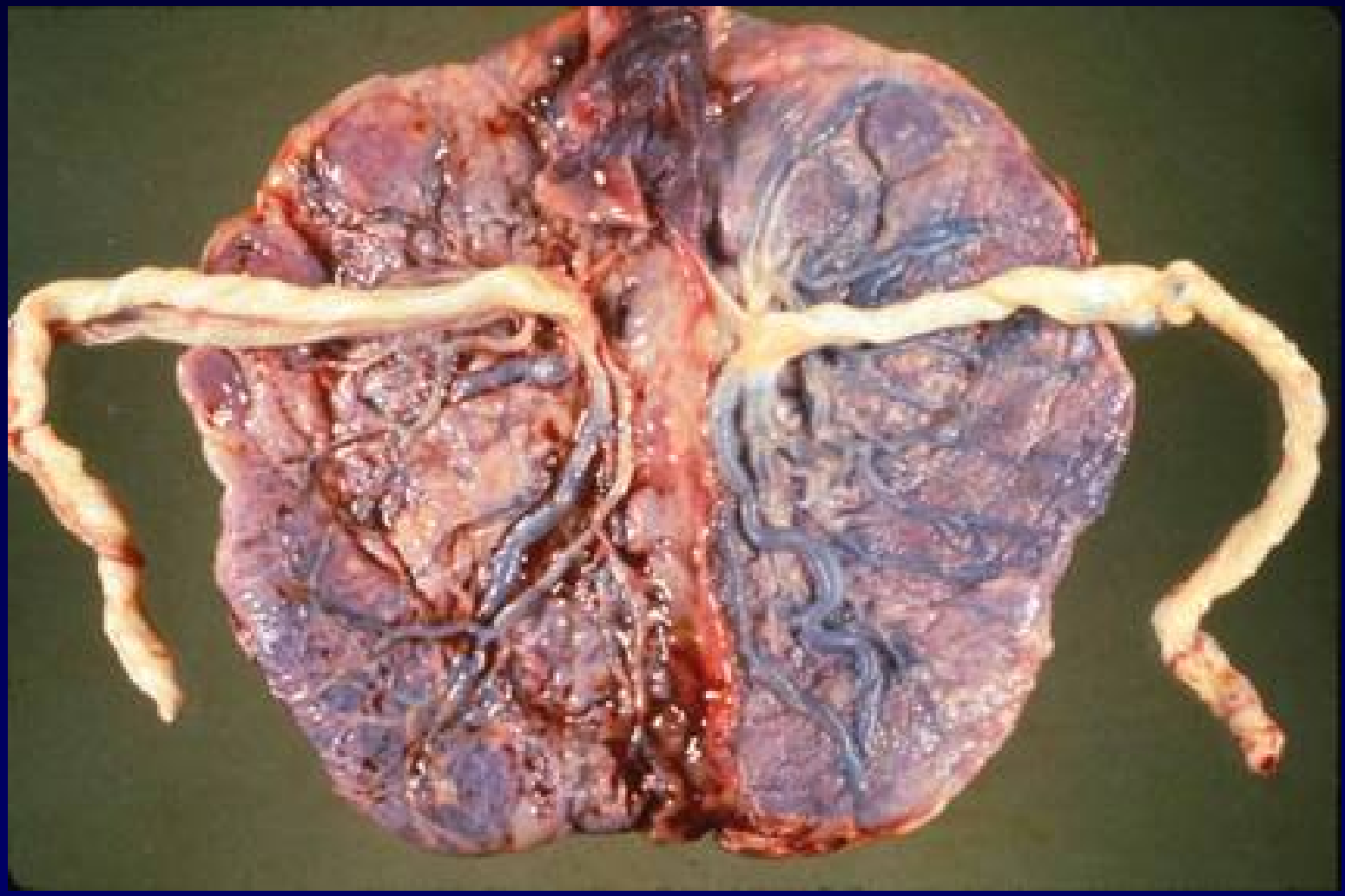
Thick, opaque dividing membranes

Dichorionic Placentation



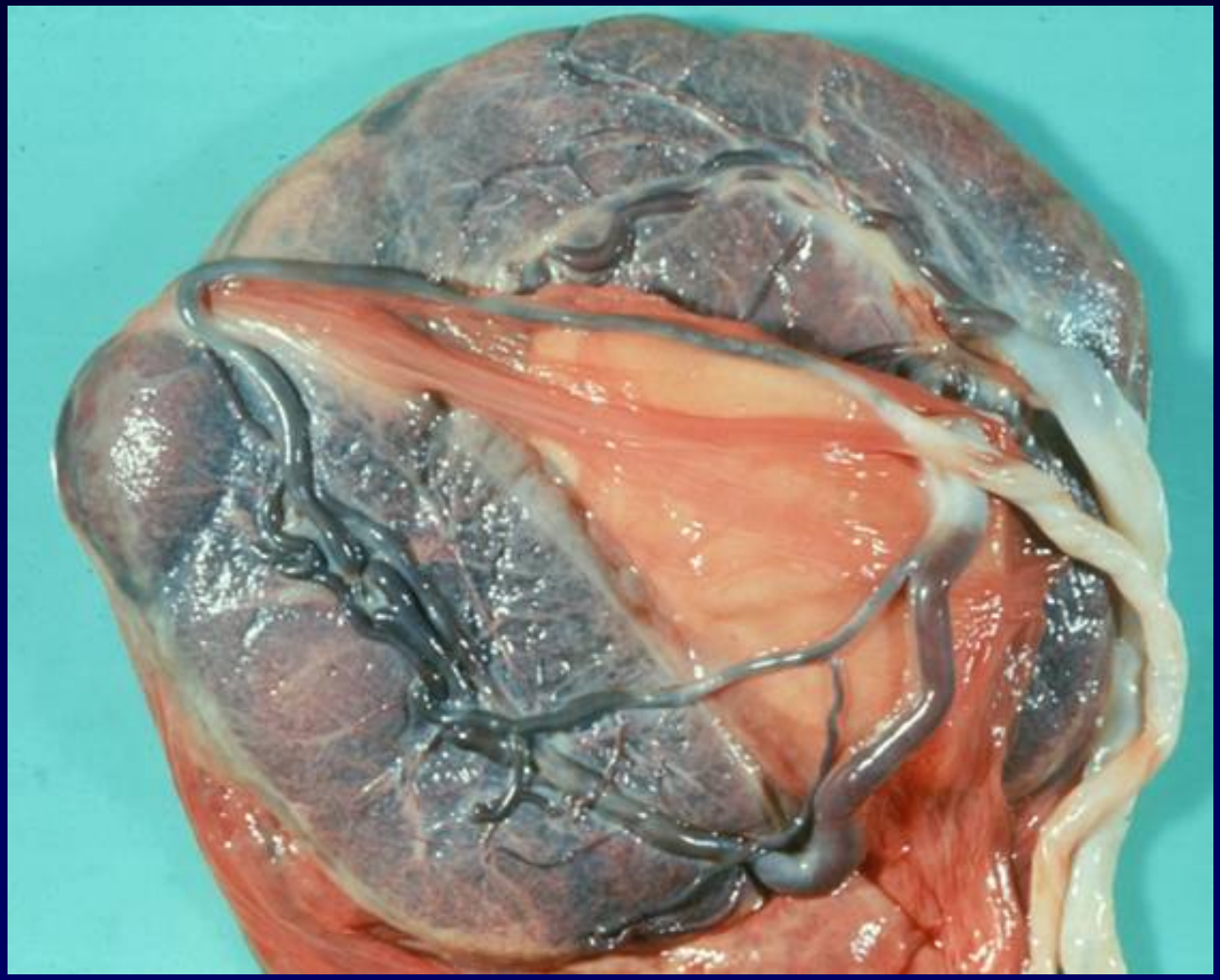
Fused amnion and chorion

Dichorionic Placentation



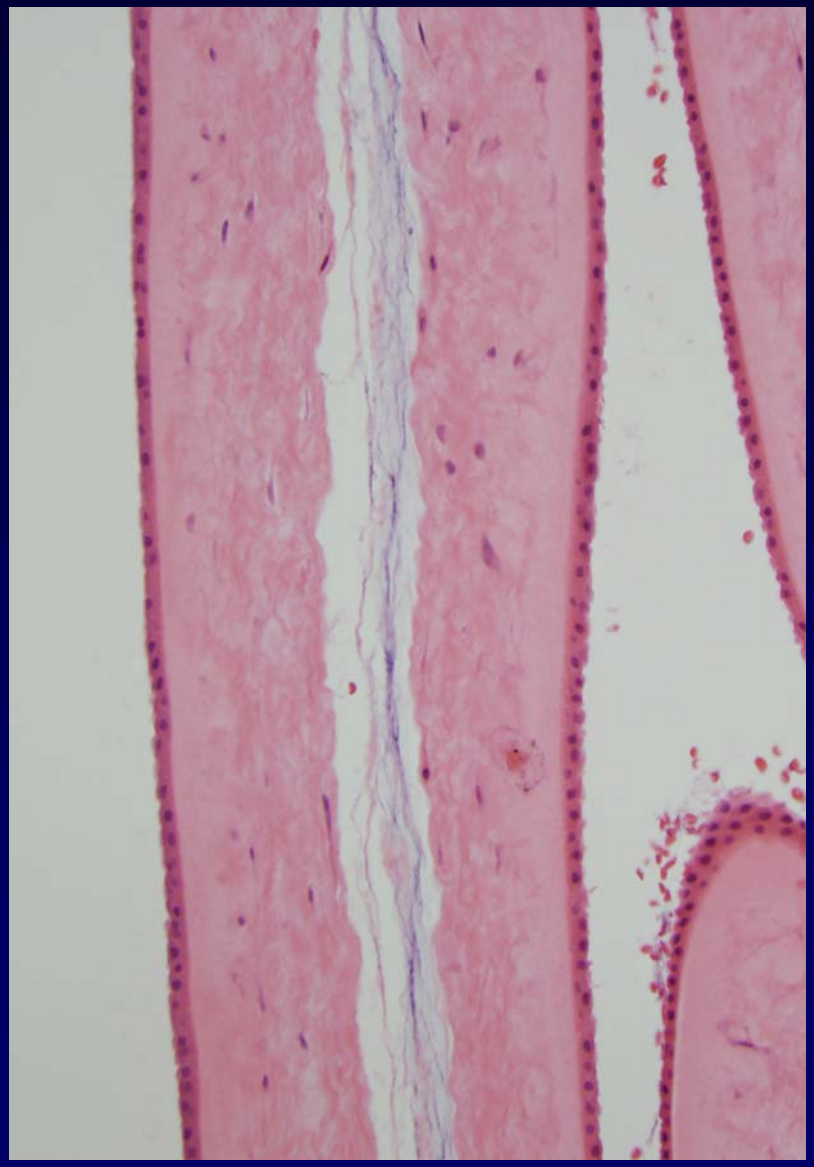
Fetal vessels approach but do not cross septum

Monochorionic Placentation



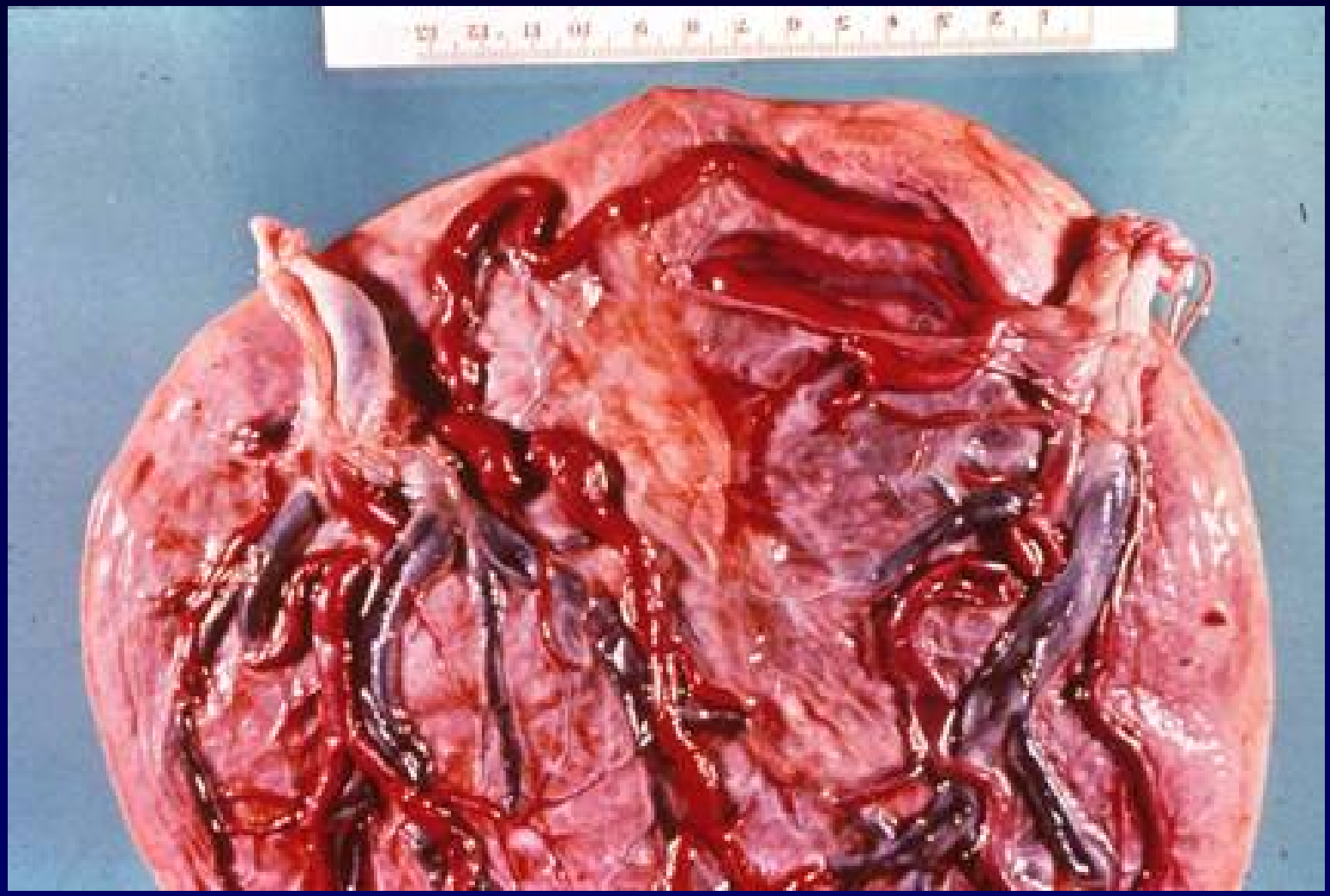
Thin, translucent dividing membranes
Vascular anastomoses

Monochorionic Placentation



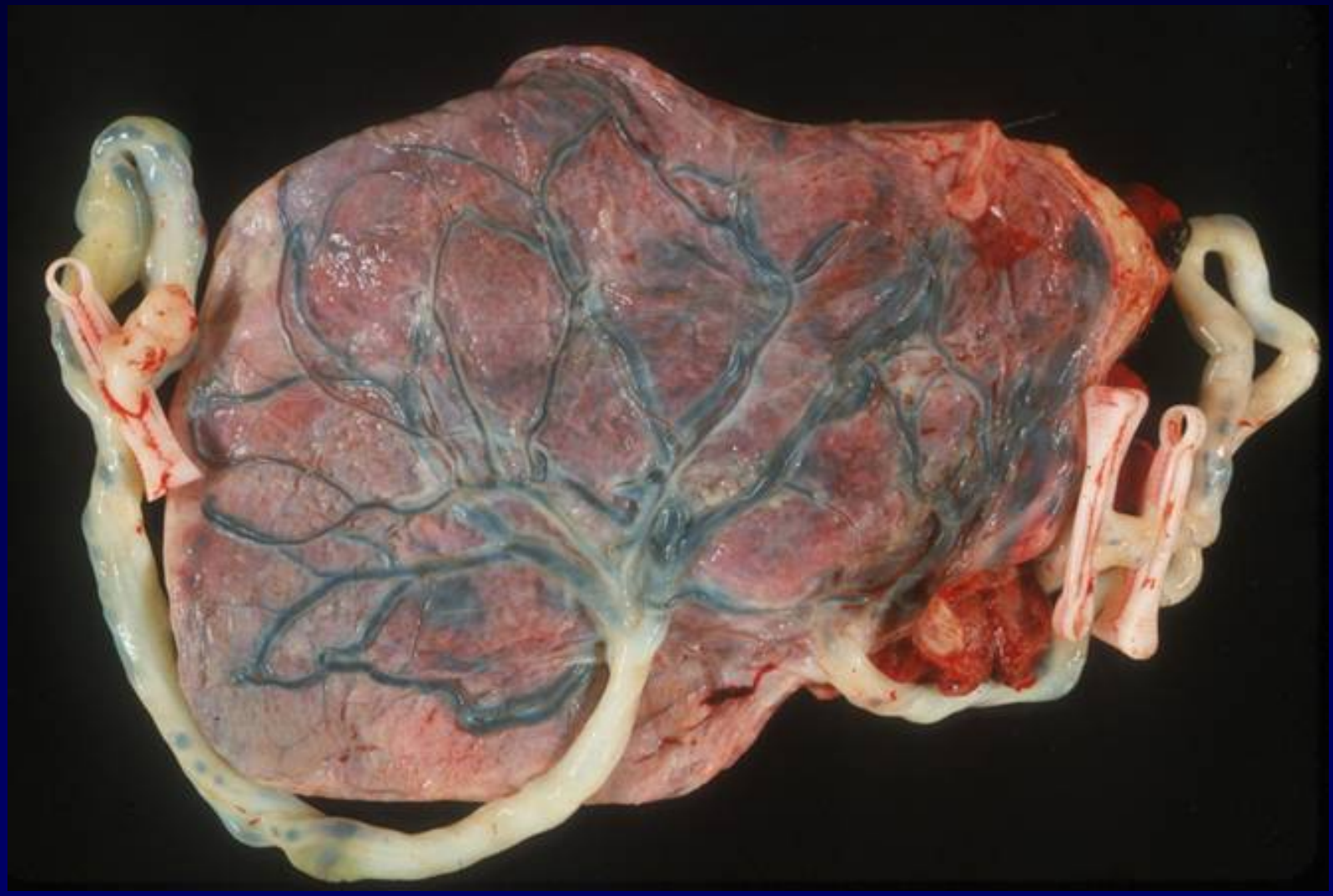
Fused amnion only

Monochorionic Placentation



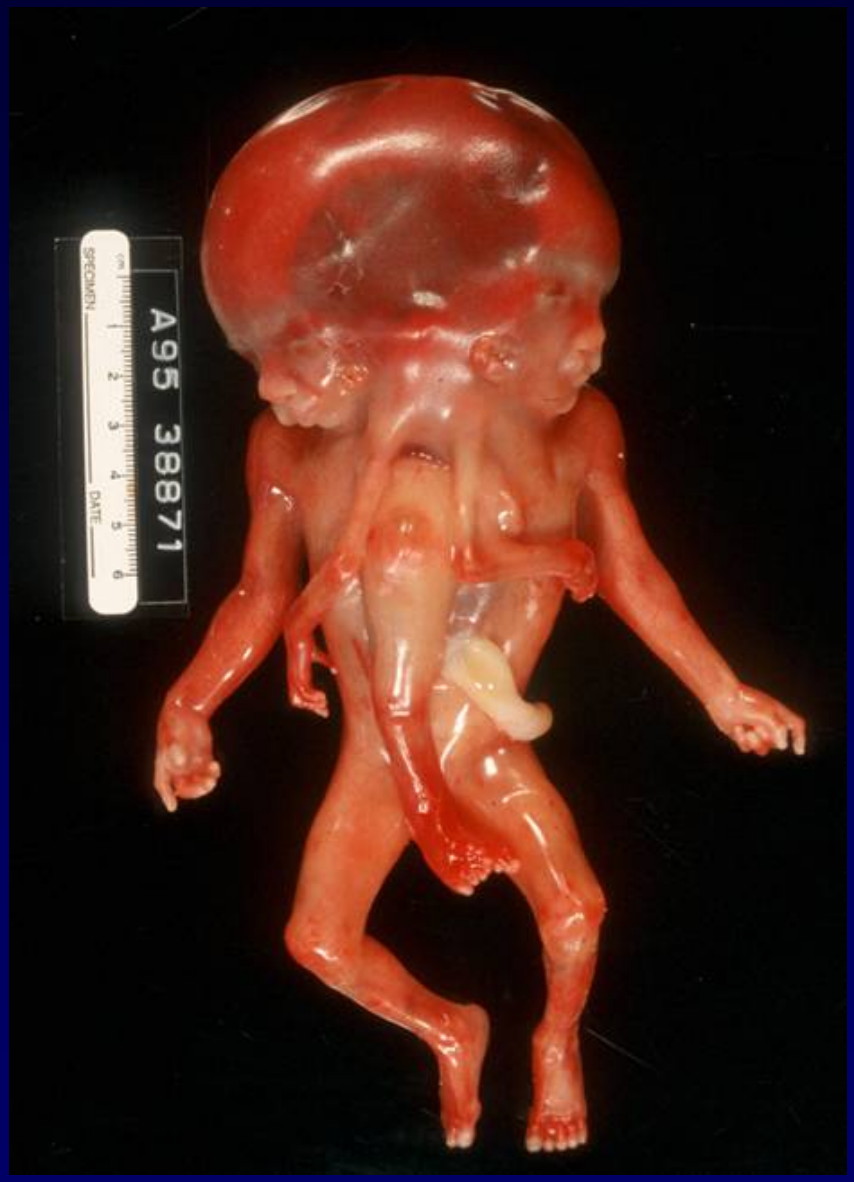
Vascular anastomoses

Monoamniotic Placentation

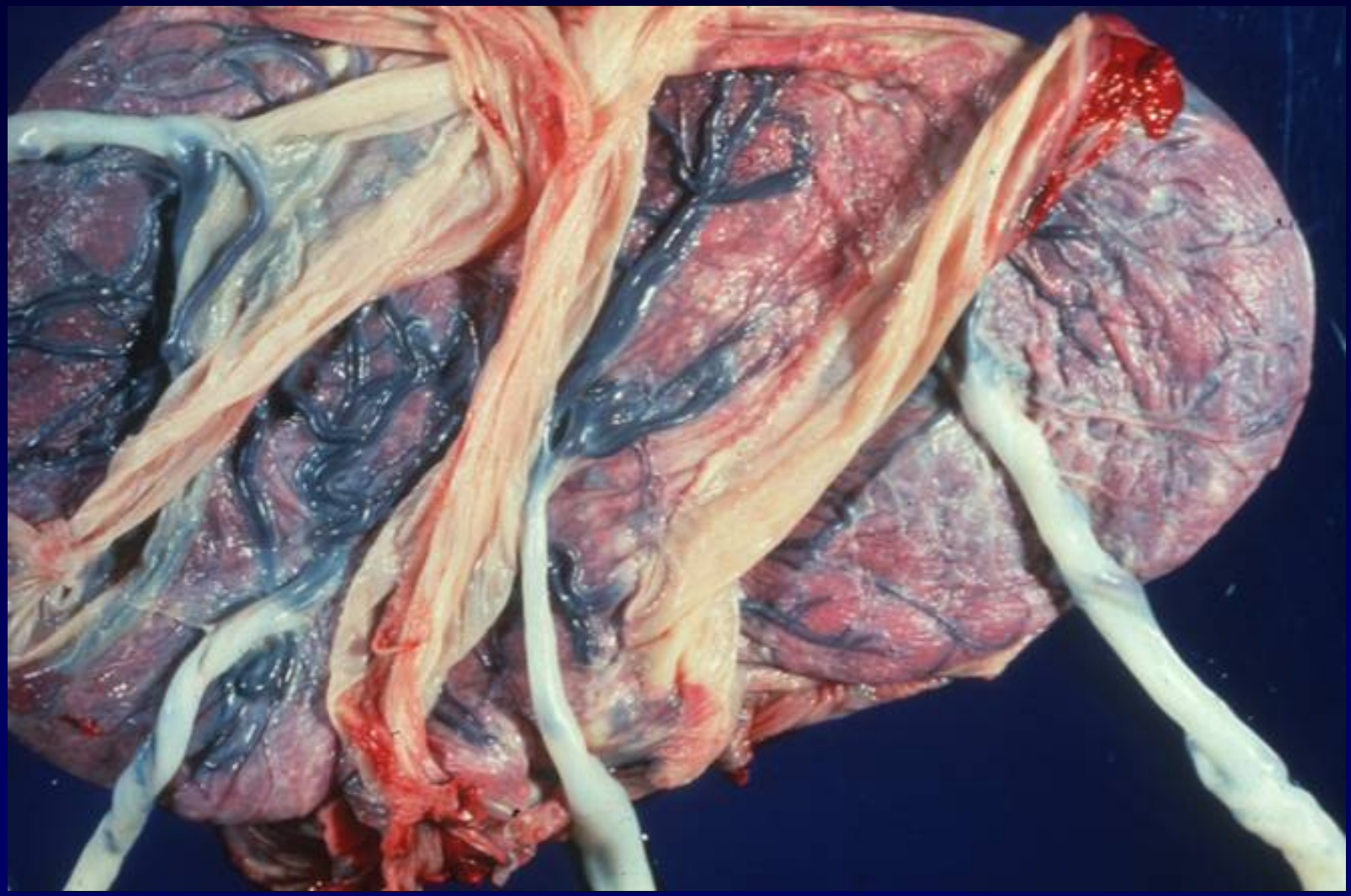


Single sac, no dividing membranes

Conjoined Twins



Higher Order Multiple Gestations



Quadruplet placenta

Multiple Gestations

Complications more common in twins vs. singletons

- Low birth weight
- Prematurity
- Anomalies, malformations
- Cerebral palsy

Multiple Gestation Complications

	MC	DC
Loss < 24 wks	12.2%	1.8%
Perinatal mortality	2.8%	1.6%
Delivery < 32 wks	9.2%	5.6%
Low BW	7.5%	1.7%
Discordant growth	11.3%	12.1%

Monoamniotic twins - 28% to 70% mortality due to cord accidents, preterm delivery

Multiple Gestation

Complications specific to twins:

- Twin-twin transfusion syndrome (TTTS)
- Discordant fetal growth
- Acardiac twinning
- Death in utero of one twin

Case 7

This twin gestation was complicated by the development of polyhydramnios and discordant fetal growth documented on ultrasound at 26 weeks. The infants were delivered at 33 weeks by Cesarean section. Twin A weighed 2400 gm (hematocrit 85%). Twin B weighed 2100 gm (hematocrit 18%). At four years, both twins are severely handicapped.

Twin-Twin Transfusion Syndrome

- See in 15% of MC twins
- 90% mortality if untreated
- Chronic imbalance of blood flow
  - Donor - hypovolemia, oliguria, oligohydramnios
    - Anemia, hypoglycemia, pale organs
  - Recipient - polyuria, polyhydramnios, hydrops
    - Heart failure, jaundice, thromboses, kernicterus
  - Fetuses usually discrepant sizes

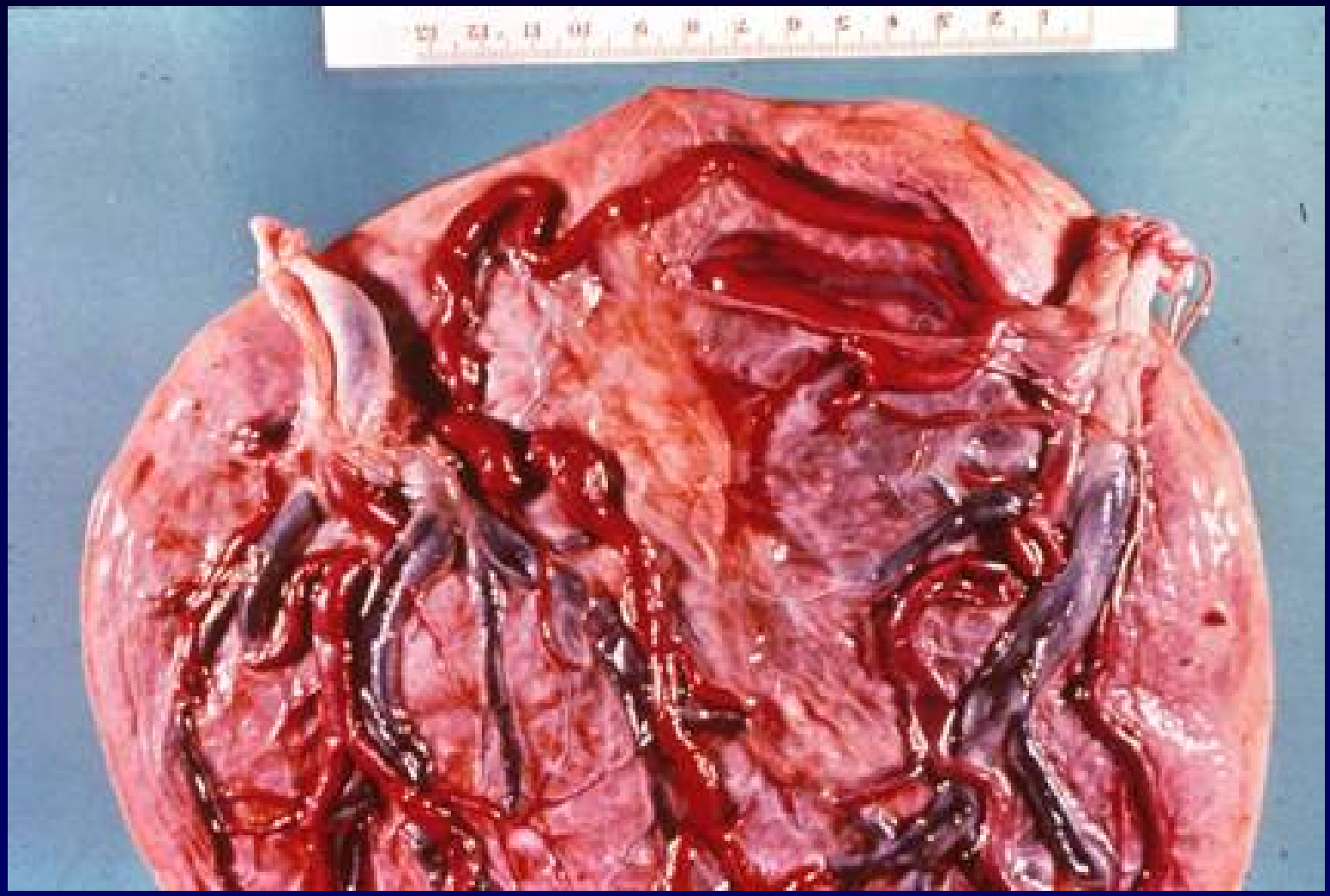
Twin-Twin Transfusion Syndrome

Twin-Twin Transfusion Syndrome

Pathogenesis related to vascular anastomoses

- Artery-artery - superficial, bidirectional
- Vein-vein - superficial, bidirectional
- Artery-vein - deep, unidirectional
  - Clue to A-V is unpaired superficial artery or vein
- Presence of A-A may be protective

Vascular Anastomoses



Twin-Twin Transfusion Syndrome

Other factors are also important

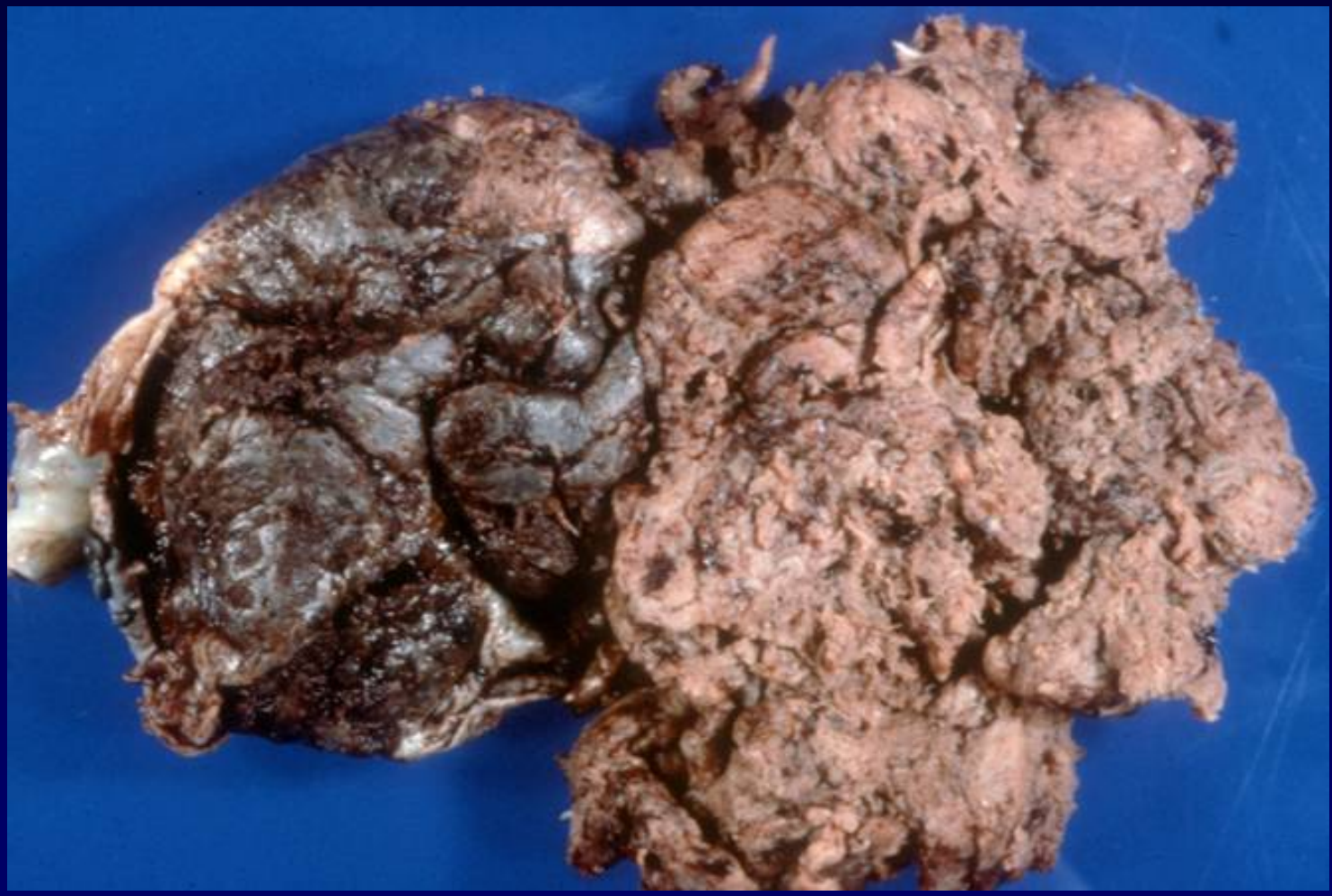
- Velamentous cord insertion
- Placental dysfunction
- Death of one twin in utero
- Acute shifts in blood flow during delivery

Twin-Twin Transfusions Syndrome

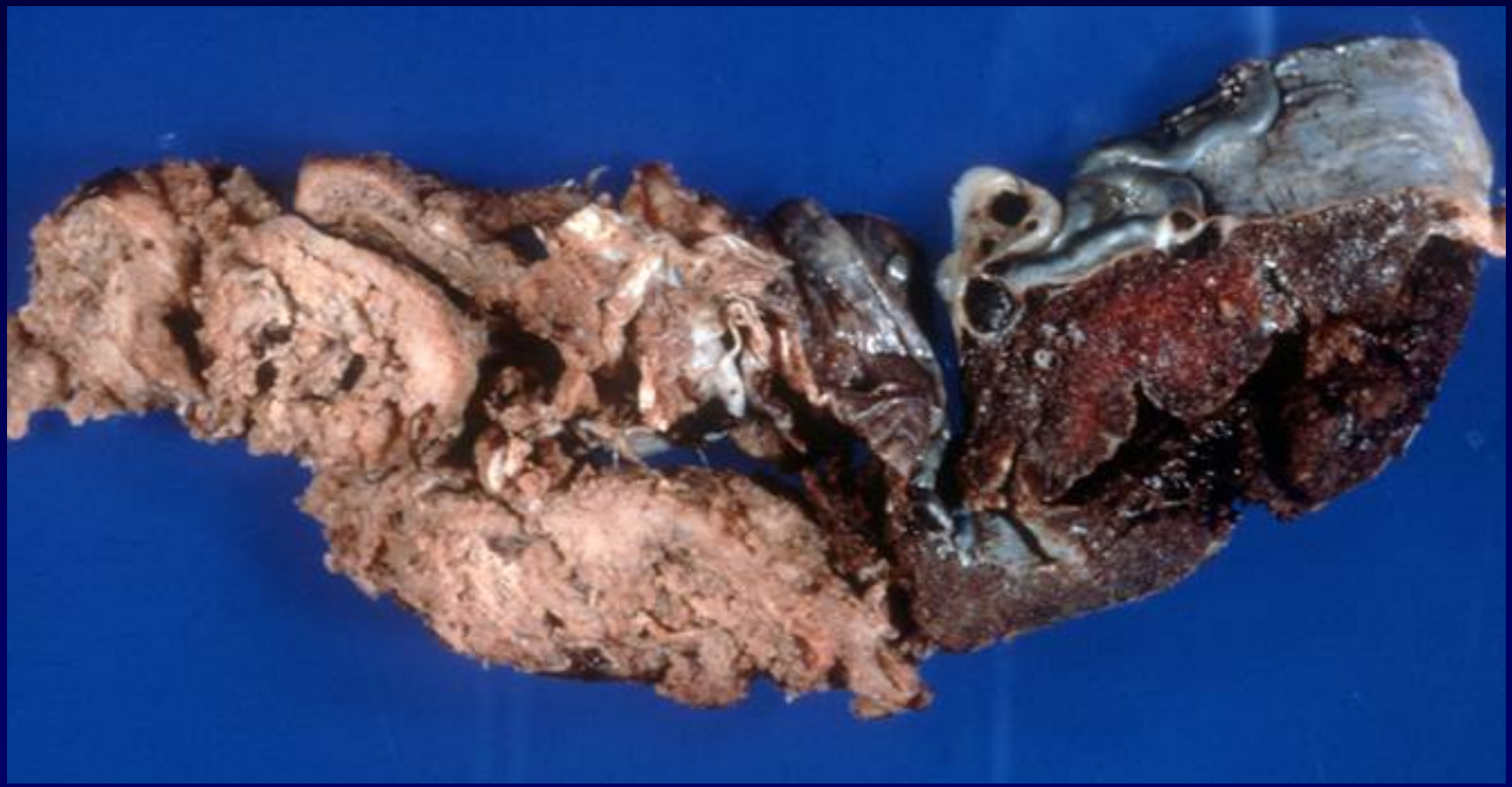
Placental features

- Donor
  - Large, bulky, pale
  - Edematous villi, ↑ nucleated RBCs
- Recipient
  - Small, firm
  - Congested villi

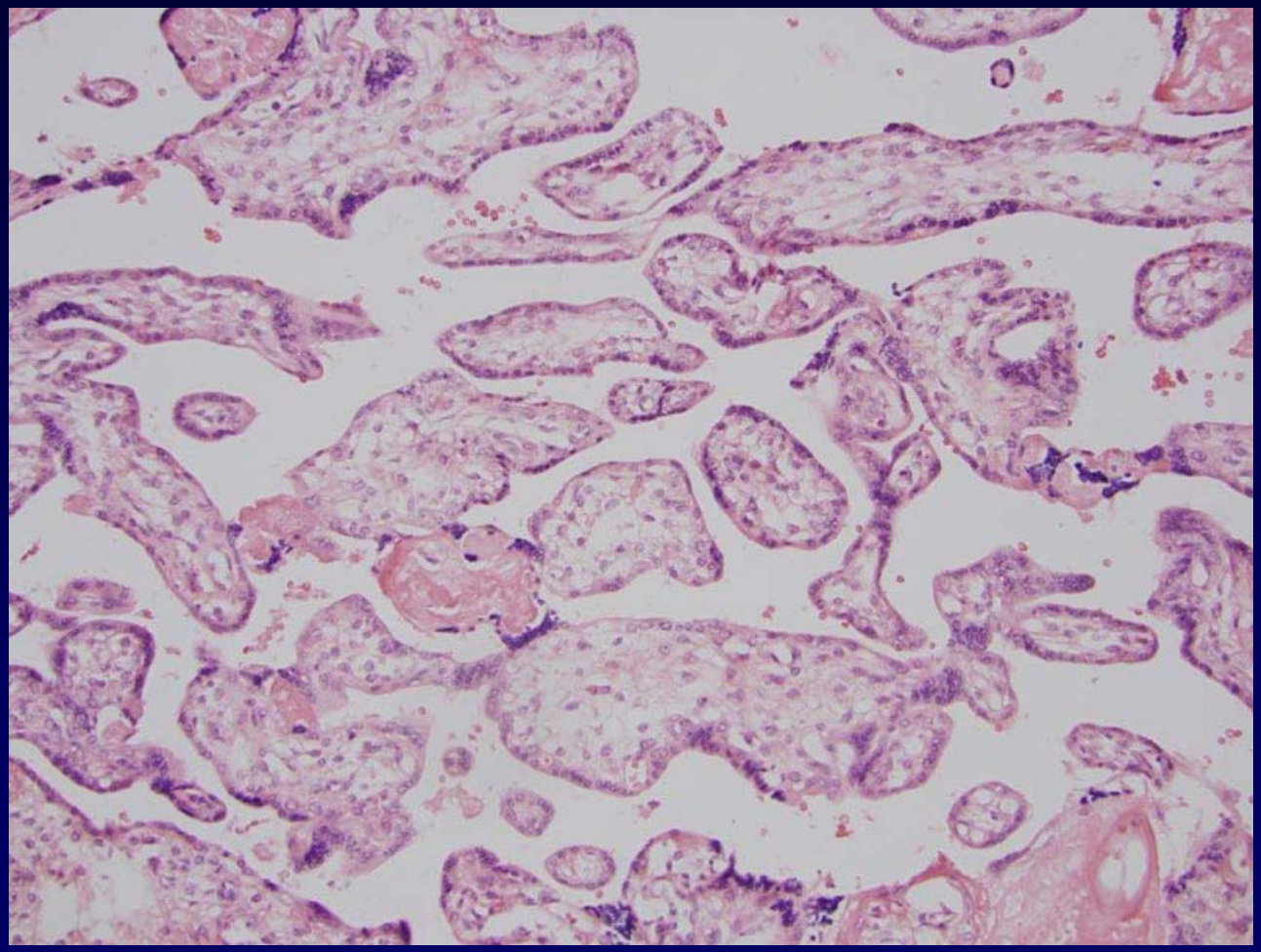
Twin-Twin Transfusion Syndrome



Twin-Twin Transfusion Syndrome

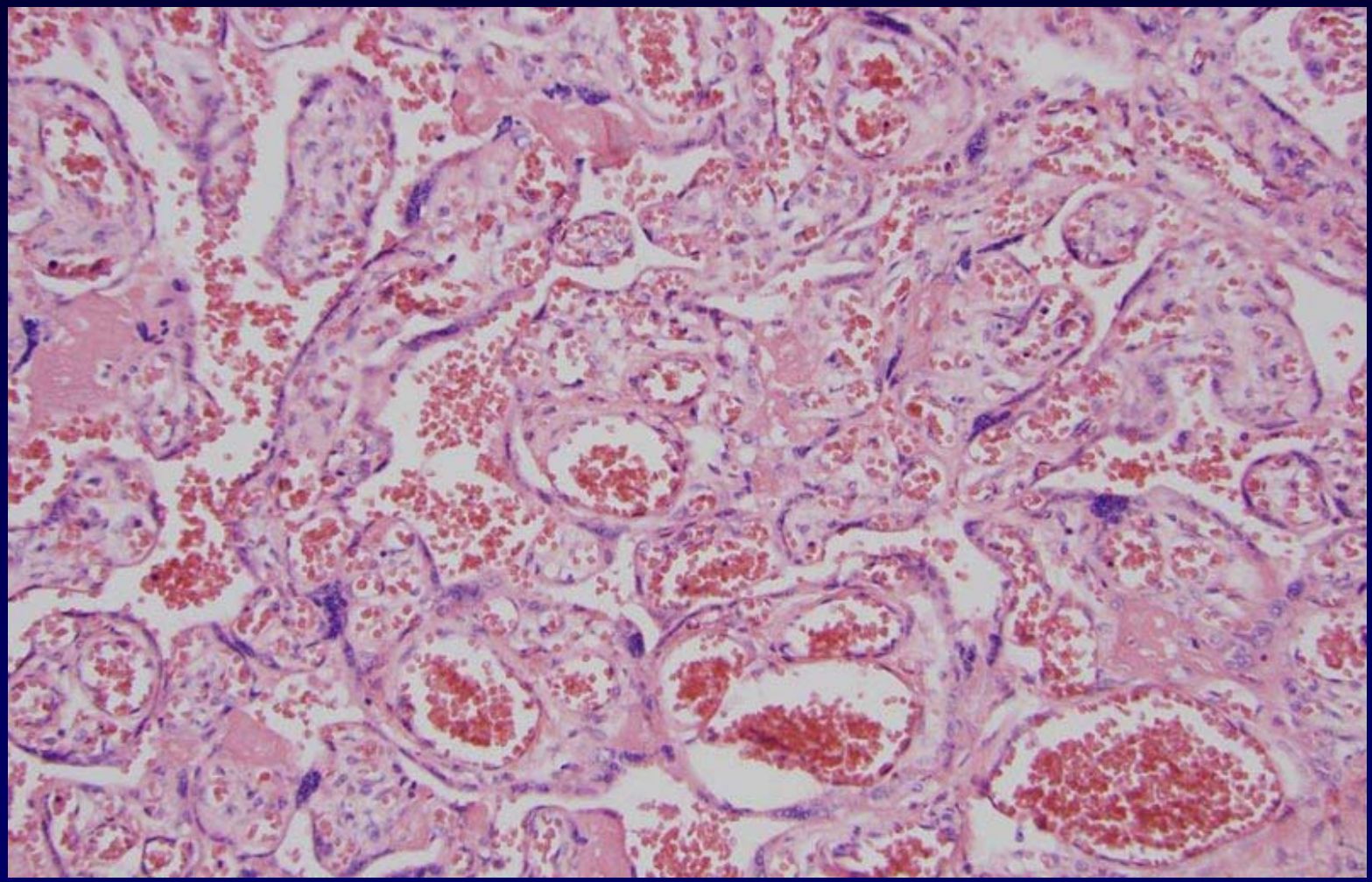


Twin-Twin Transfusion Syndrome



Donor with large, edematous villi

Twin-Twin Transfusion Syndrome



Recipient with congested villi

Twin-Twin Transfusion Syndrome

Treatment options - controversial

- Delivery
- Amnioreduction
- Rupture of dividing membranes
- Laser coagulation of anastomotic vessels
- Selective termination

Discordant Fetal Growth

- Difference in fetal weights > 25%
- Occurs in ~ 12% of MC and DC twins
- Mortality is greater if MC

Discordant Fetal Growth

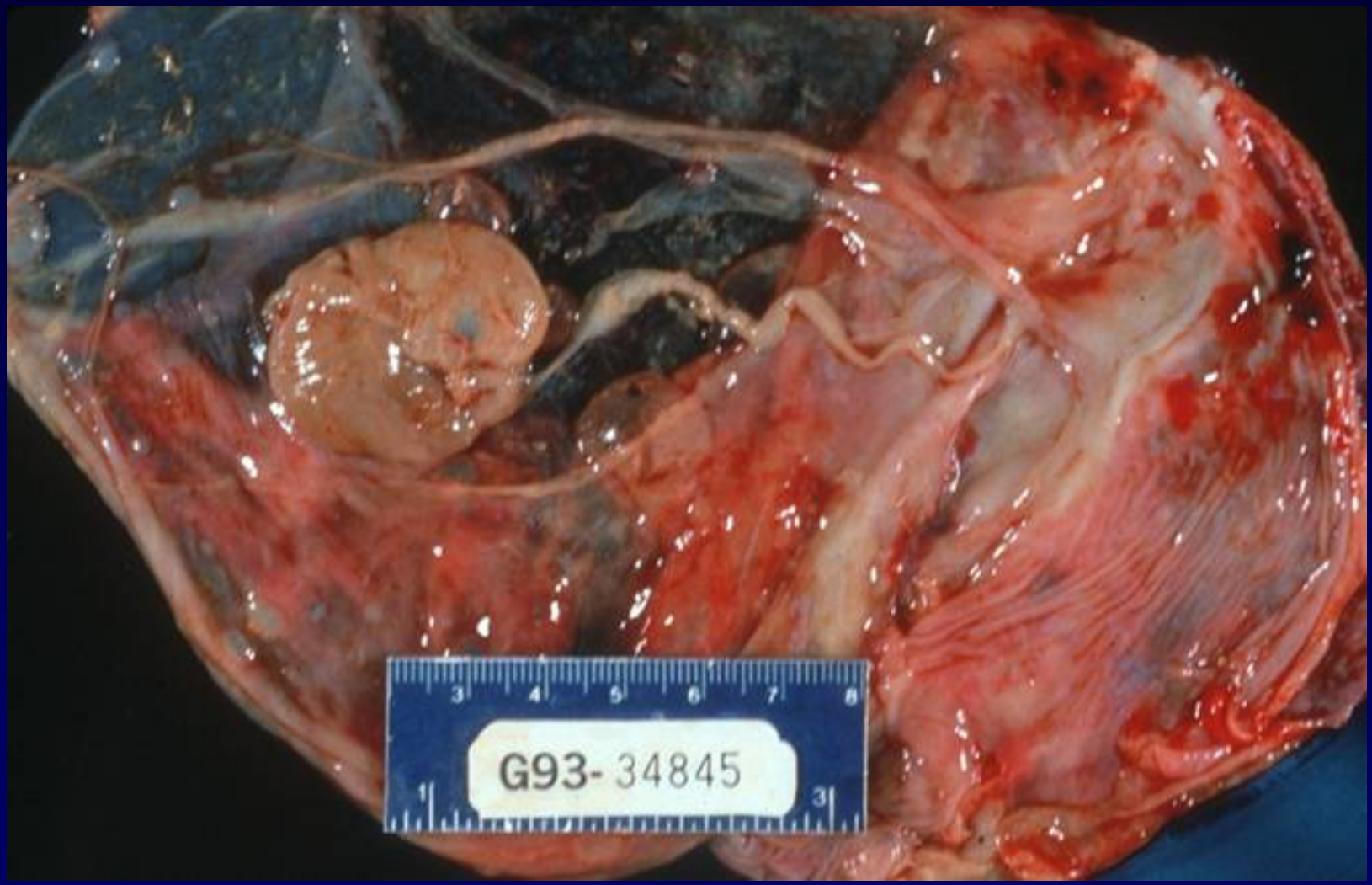
Causes of discordant fetal growth:

- Degree of placental sharing
- Quality of implantation in each territory
- Differences in angioarchitecture
- Velamentous cord insertion

Fetal Death In Utero of One Twin

- Vascular resistance of dead twin ↓
- Blood flows from live twin to dead twin
- Sudden hypotension, hypoperfusion of organs
- Severe morbidity in live twin

Fetal Death In Utero of One Twin



Mummified remnant of early embryo

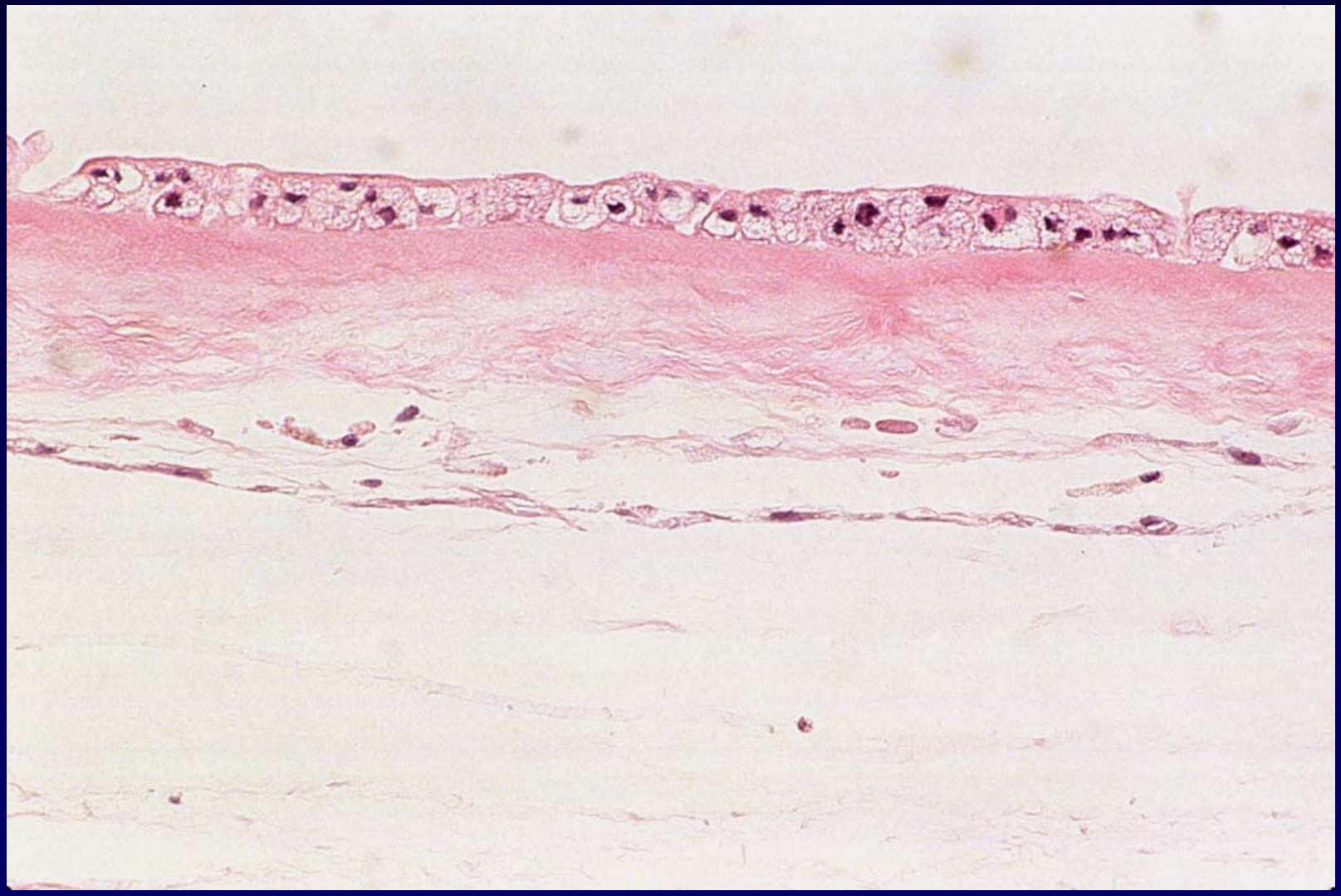
Pathology of the Fetal Membranes

- Changes secondary to meconium
- Diffuse chorioamniotic hemosiderosis
- Squamous metaplasia
- Amnion nodosum
- Amniotic bands

Case 8

This 20 year old G1 P0 woman had an intrauterine pregnancy at 35 weeks gestational age complicated by severe fetal intrauterine growth restriction and gastroschisis with small intestine and part of the stomach located outside the abdominal wall. She was delivered for non reassuring fetal parameters.

Gastroschisis



Gastroschisis

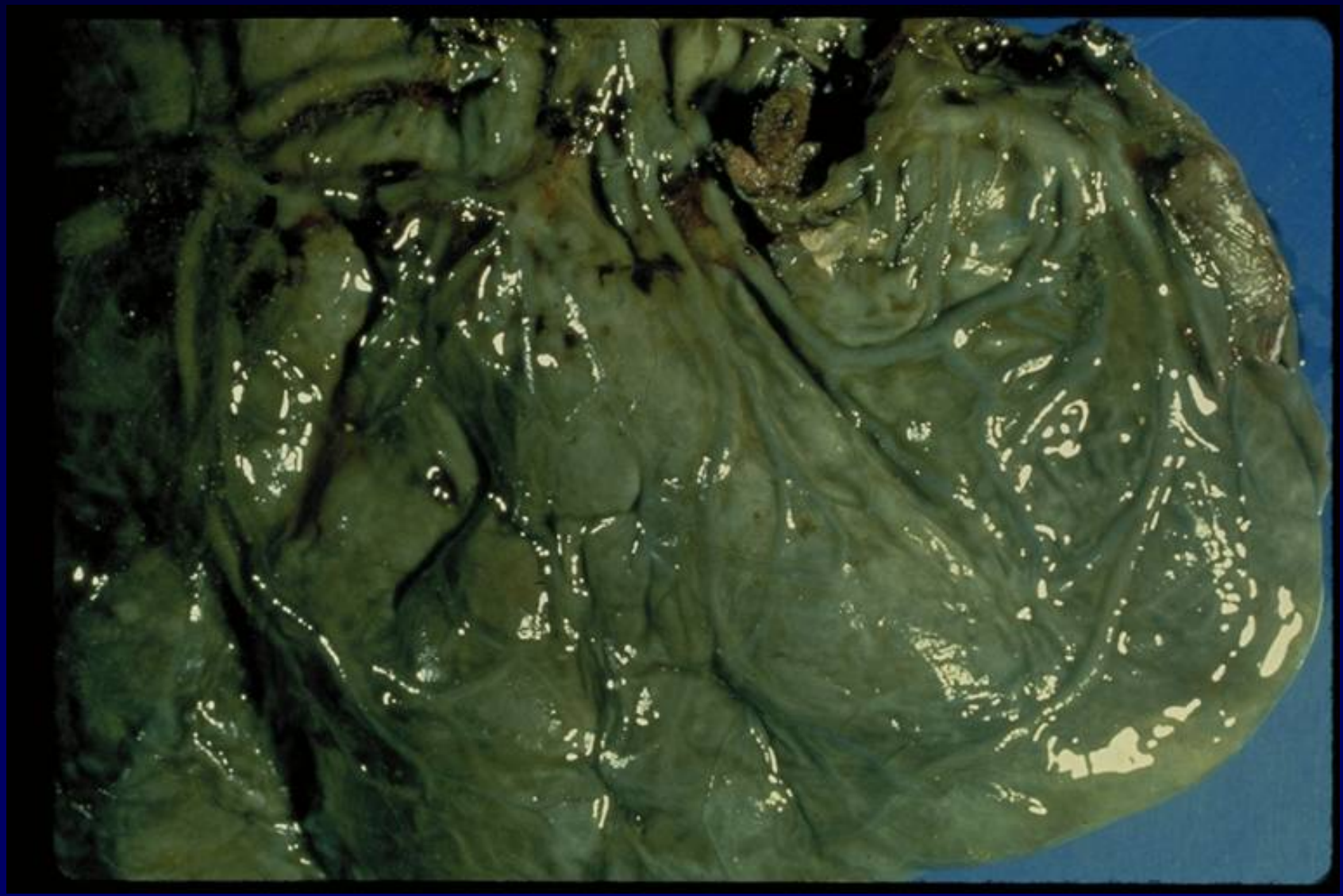
Microscopic findings

- Small vacuoles with central nucleus
- Accompanying meconium
- Vacuoles may involve chorion, decidua

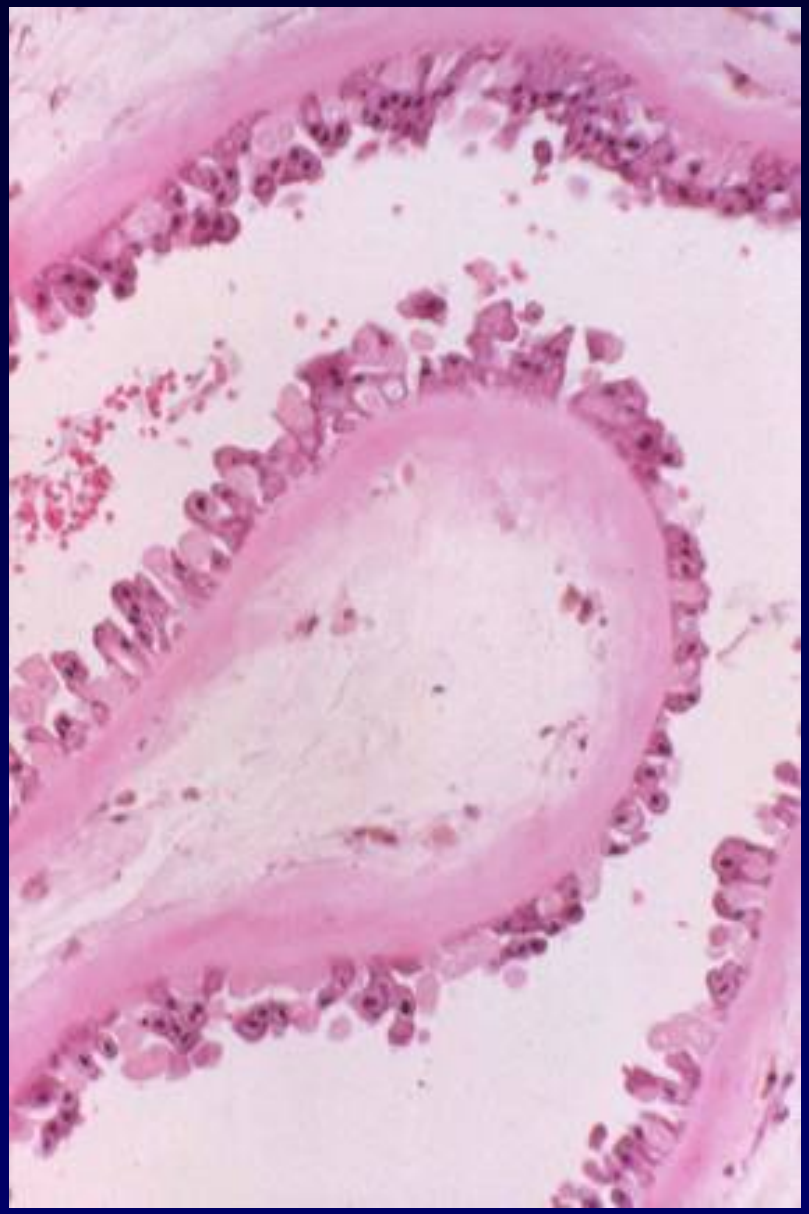
Apparently specific for gastroschisis

Material is lipid by ultrastructure

Meconium staining

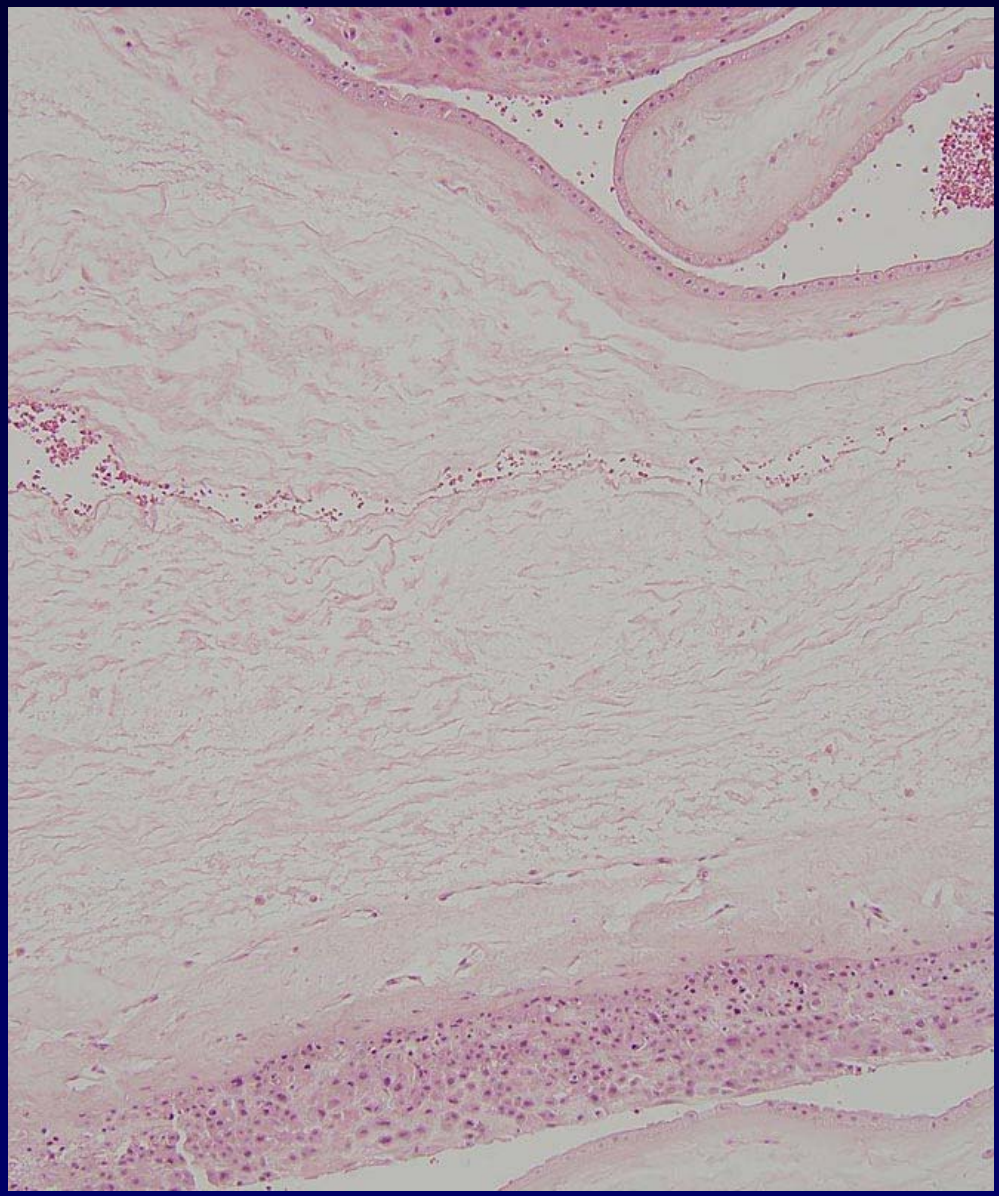


Meconium

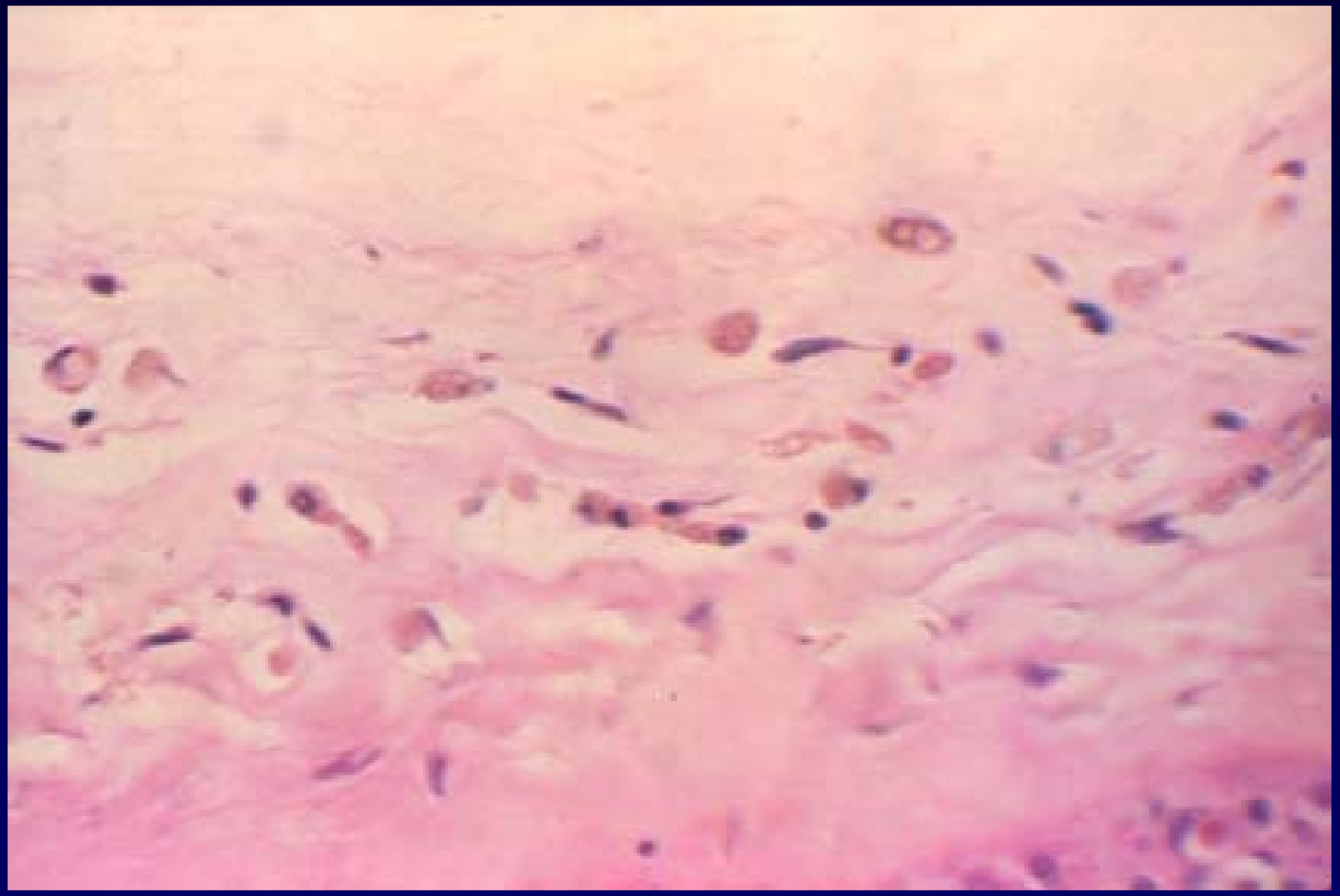


- Stratified amnion
- Pyknotic nuclei
- Pigmented macrophages

Meconium



Meconium in membranes



Macrophages in membranes stuffed with meconium

	Gross Features	Clinical Features
Acute	blue-green glistening residual meconium	usually normal
Subacute	dark slippery, edematous	mec aspiration syndrome
Chronic	muddy brown dull	prenatal hypoxia likely

Meconium

10 to 20% of liveborns pass meconium

- 20 to 30% are depressed at birth
- 5% are severely affected

Meconium Aspiration Syndrome

- Respiratory distress in a meconium-stained infant
- No other explanation for distress

Meconium

Meconium passage correlates with parameters of perinatal distress

- Apgars < 3 at 1 and 5 minutes
- Umbilical artery pH < 7.0
- Seizures
- Delivery room resuscitation

Meconium

Physiologic – majority do well

Adverse stimuli – require low O2

Meconium Aspiration Syndrome
do poorly

Meconium

Other effects:

- May induce vasoconstriction
- Meconium-associated vascular necrosis in umbilical cord and chorionic plate vessels
  - May really represent meconium-specific karyorrhexis
- See in < 1% of meconium-stained placentas

Membrane Pigments

Meconium

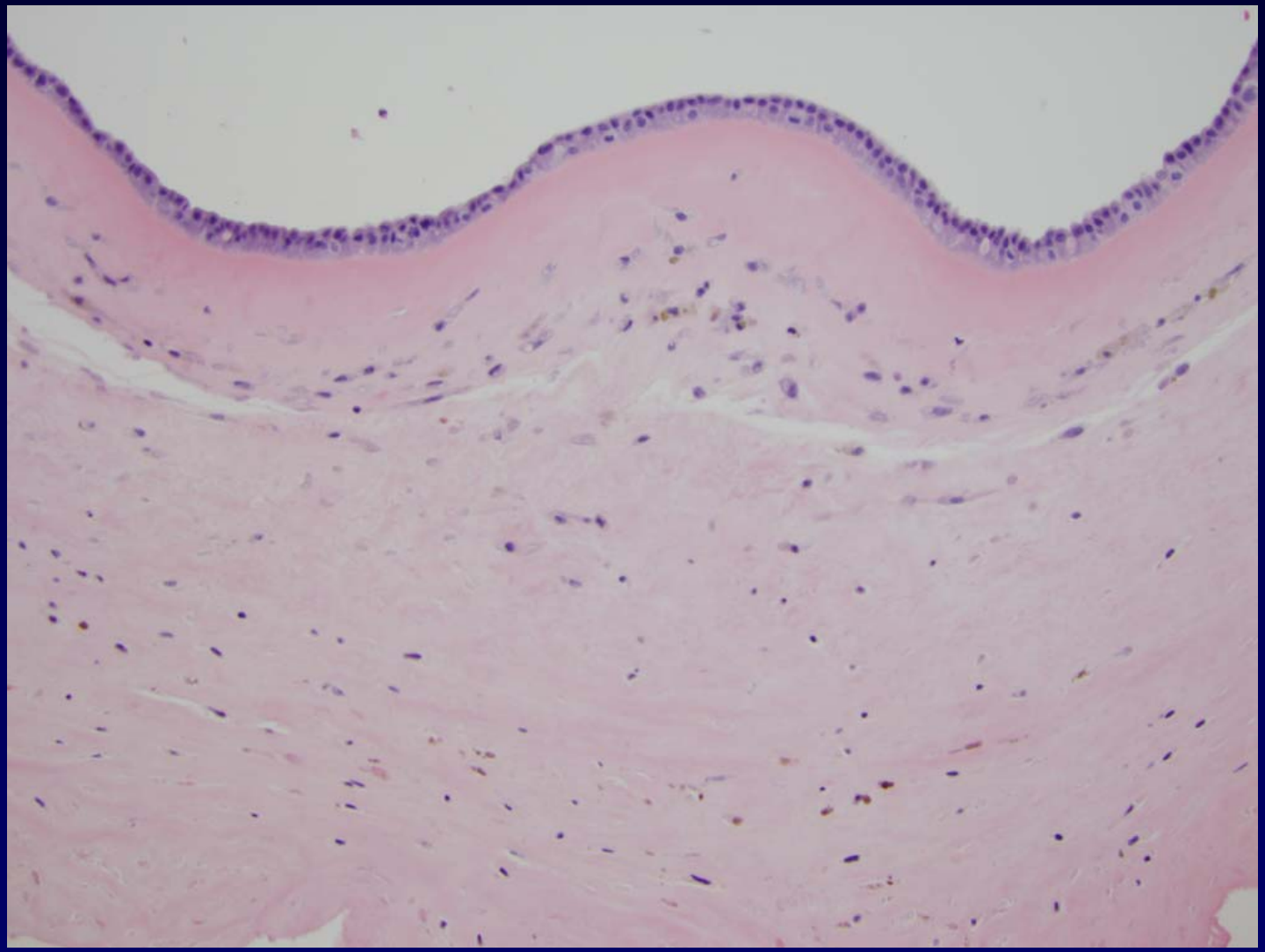
- Gross
  - green-blue
- Micro
  - yellow-green, waxy
  - Associated edema, stratification

Membrane Pigments

Hemosiderin

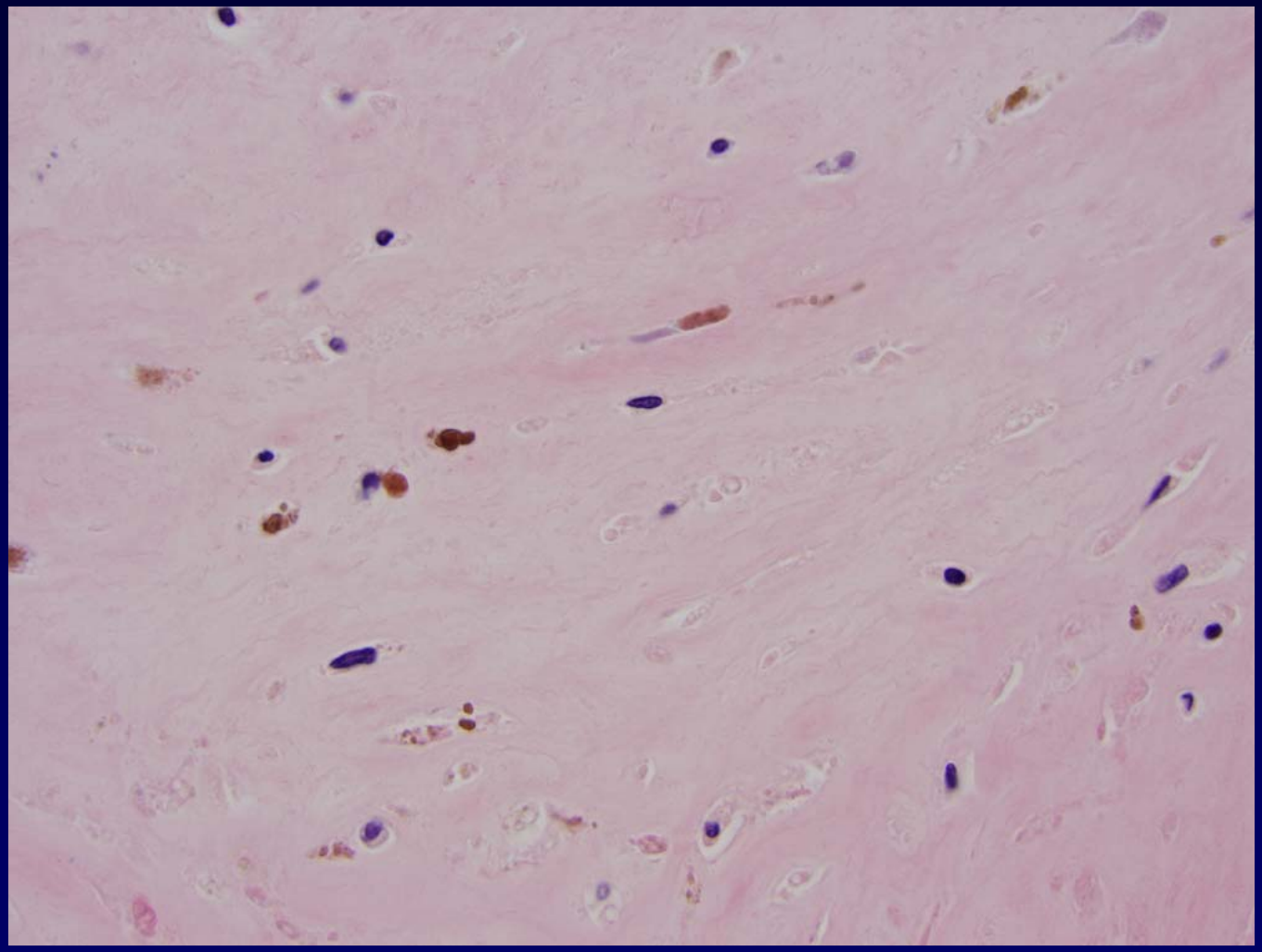
- Gross
  - Brown, green
  - Often associated blood clot
- Micro
  - Yellow-brown
  - Refractile
  - Positive on iron stain

Hemosiderin



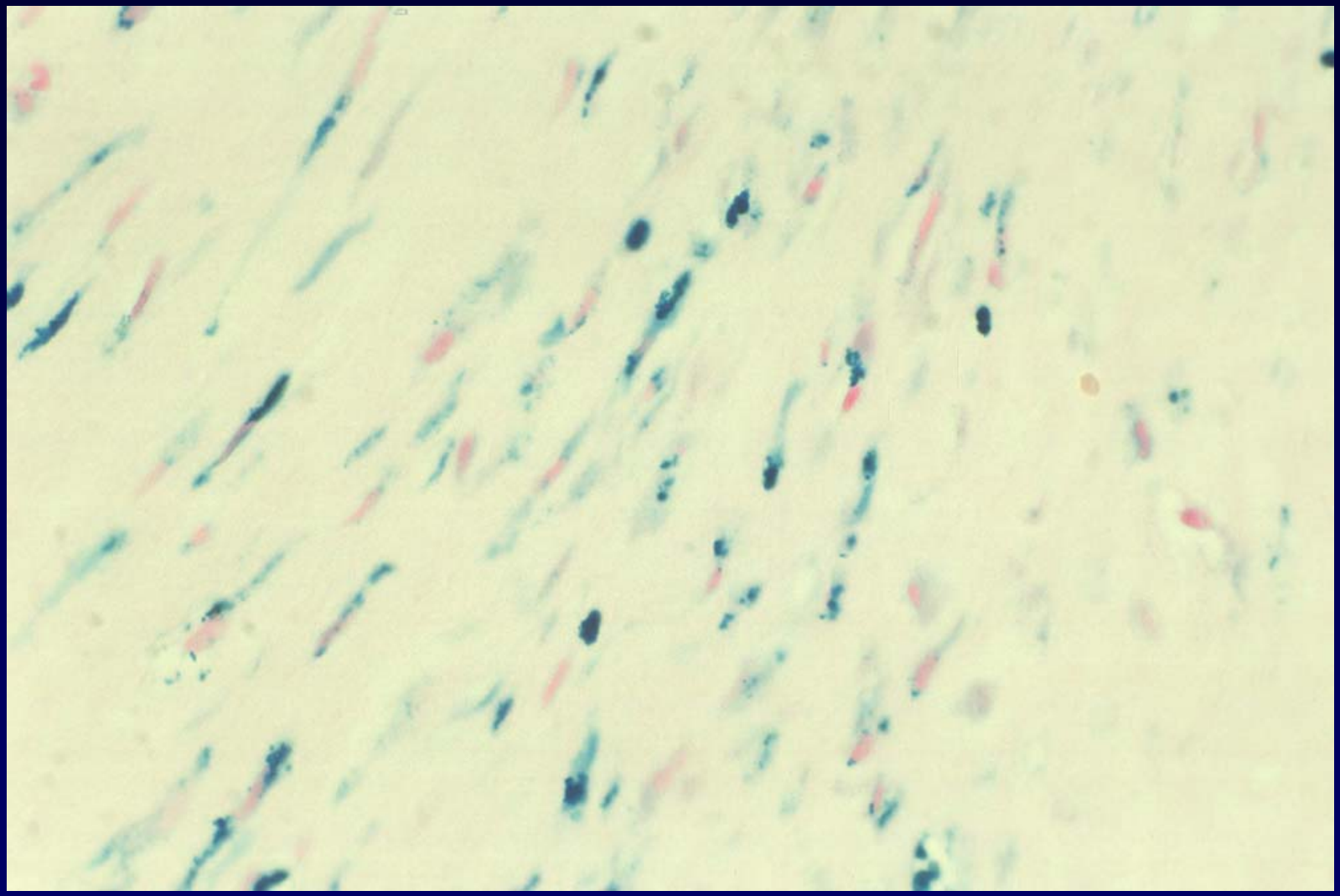
No reactive changes in amnion

Hemosiderin



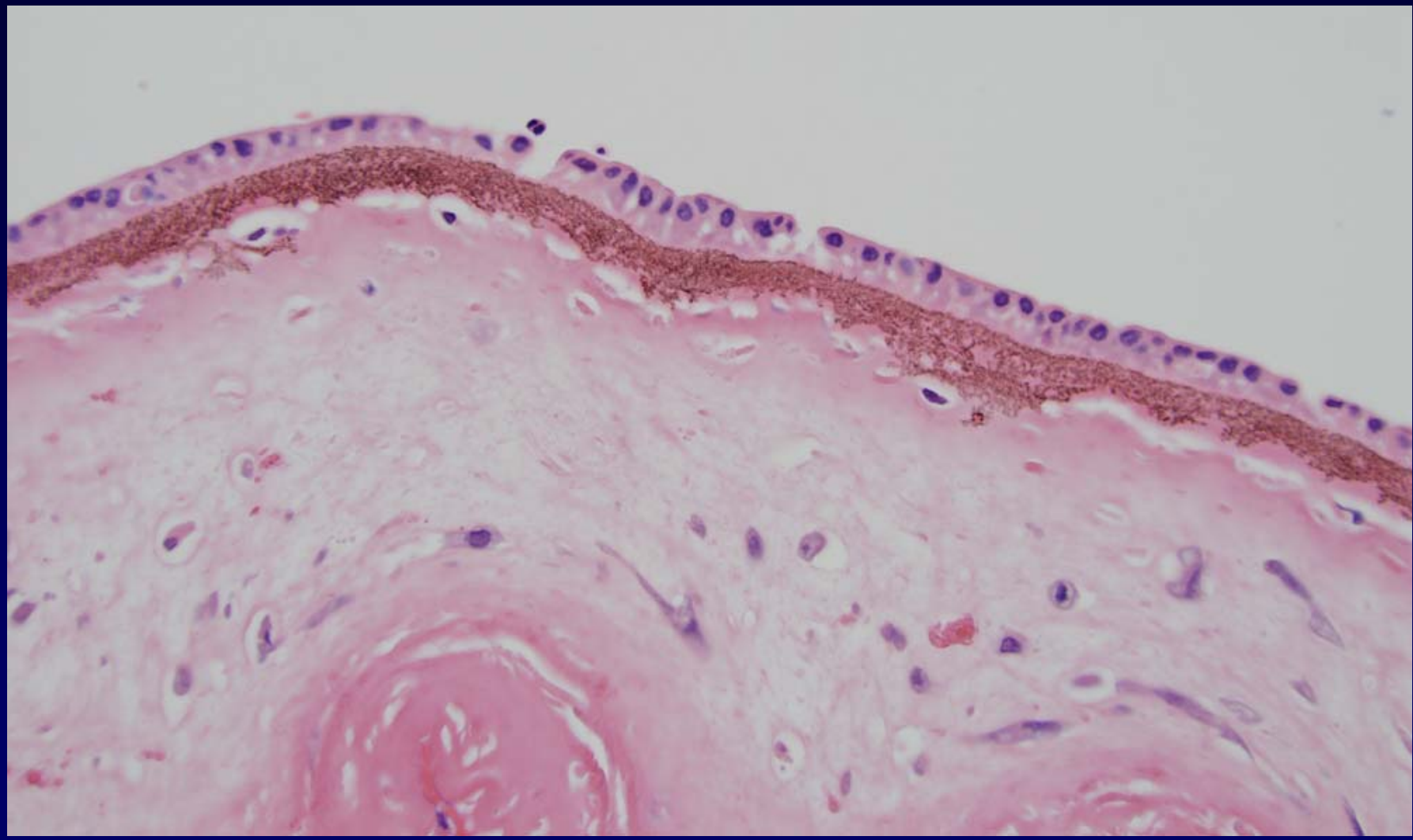
Refractile pigment

Hemosiderin



Positive Prussian Blue stain for iron

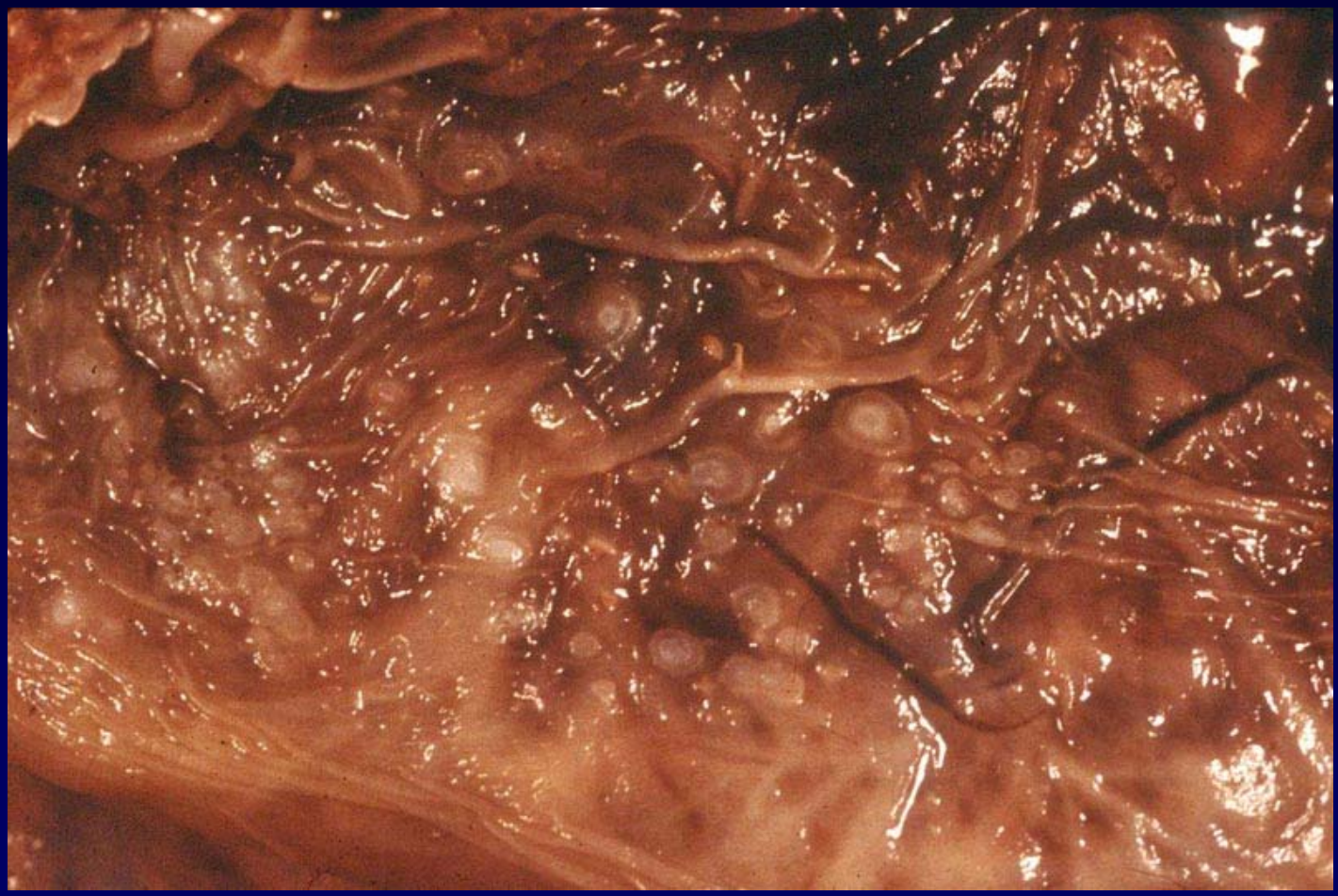
Hemosiderin



Diffuse Chorioamniotic Hemosiderosis

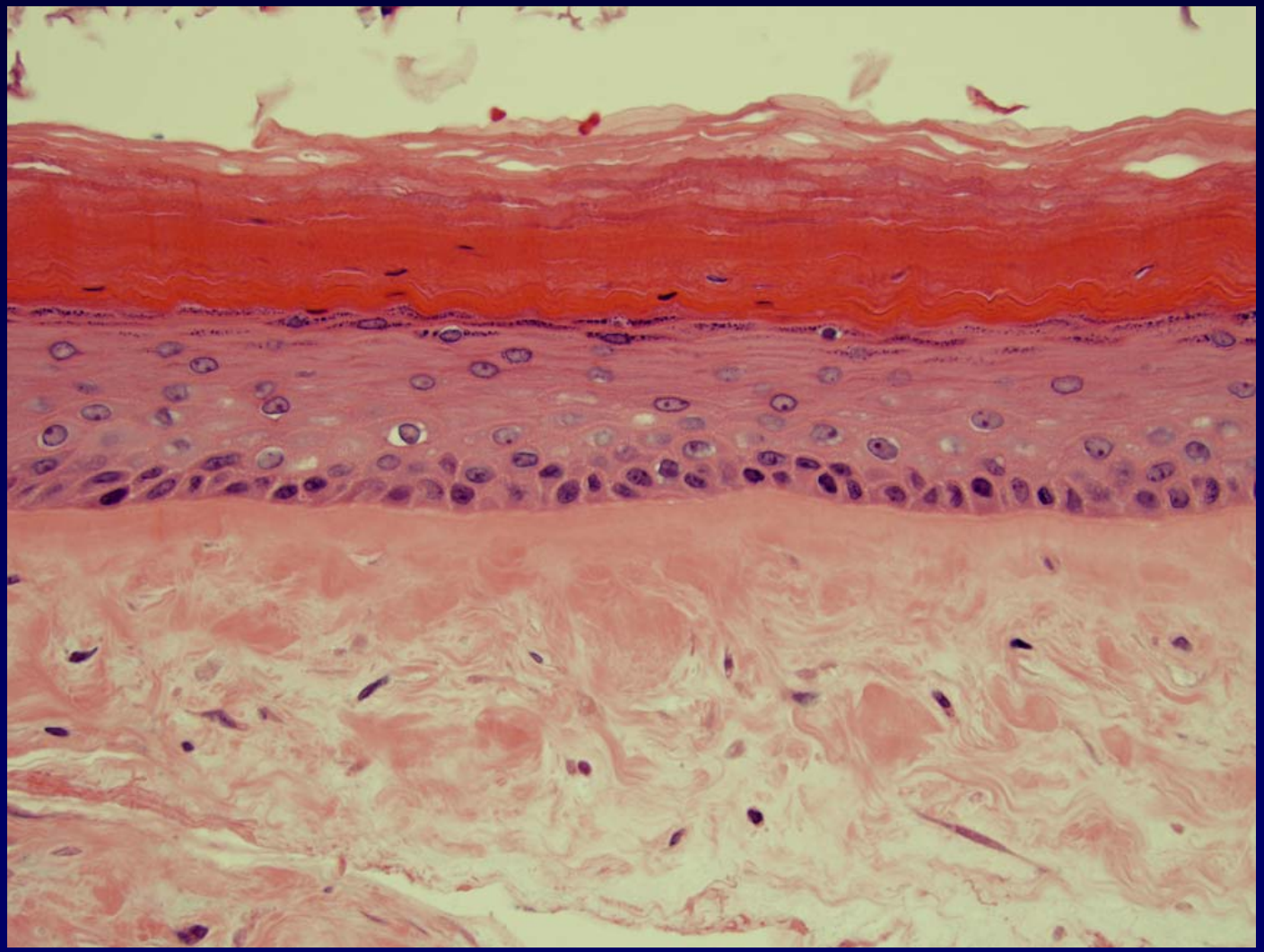
- Associated placental findings
  - Old clot
  - Circumvallation
- Associated clinical findings
  - Oligohydramnios without membrane rupture
  - Preterm delivery
  - Persistent pulmonary HTN, chronic lung disease

Squamous Metaplasia

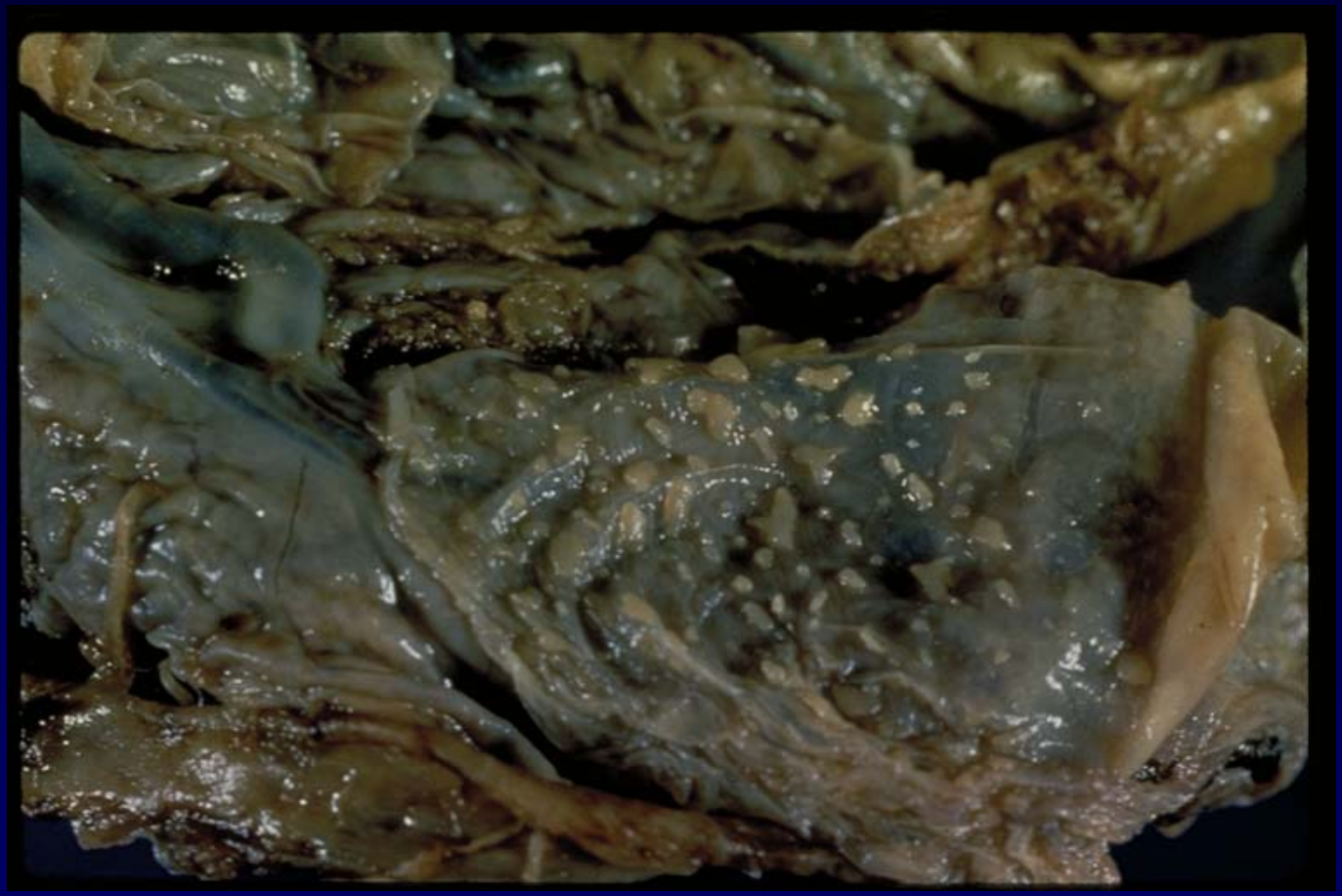


Anywhere on fetal membranes, fetal surface
Difficult to remove

Squamous Metaplasia



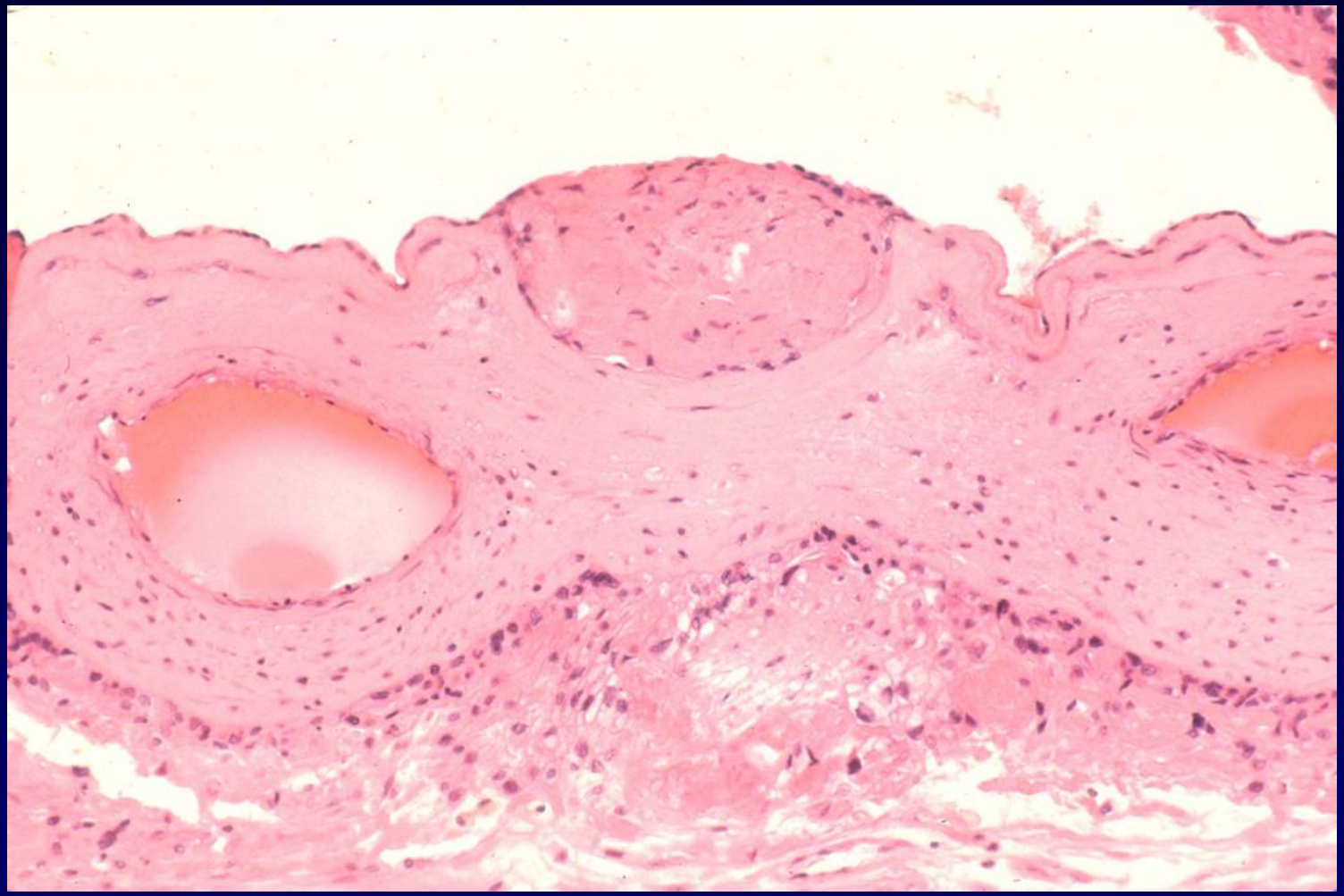
Amnion Nodosum



Associated with oligohydramnios

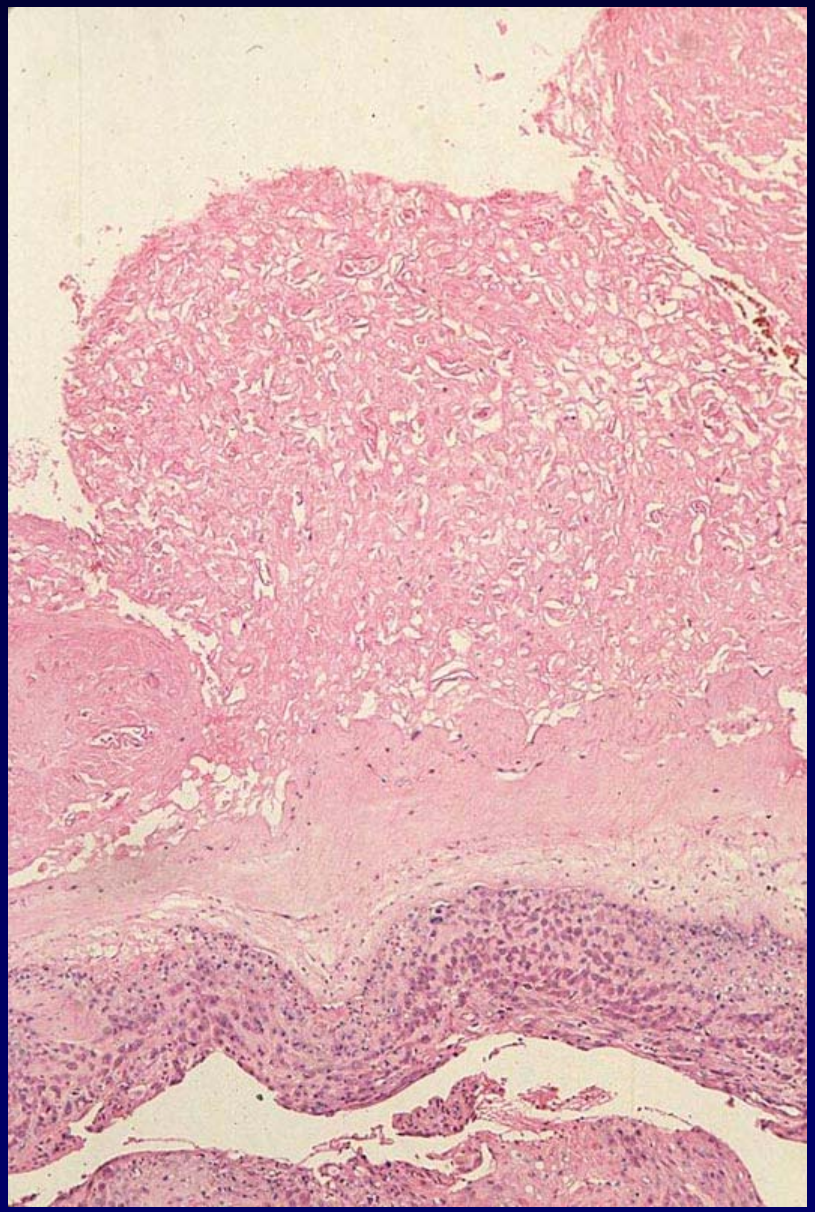
Renal anomalies, Potter's syndrome, pulmonary hypoplasia

Amnion Nodosum

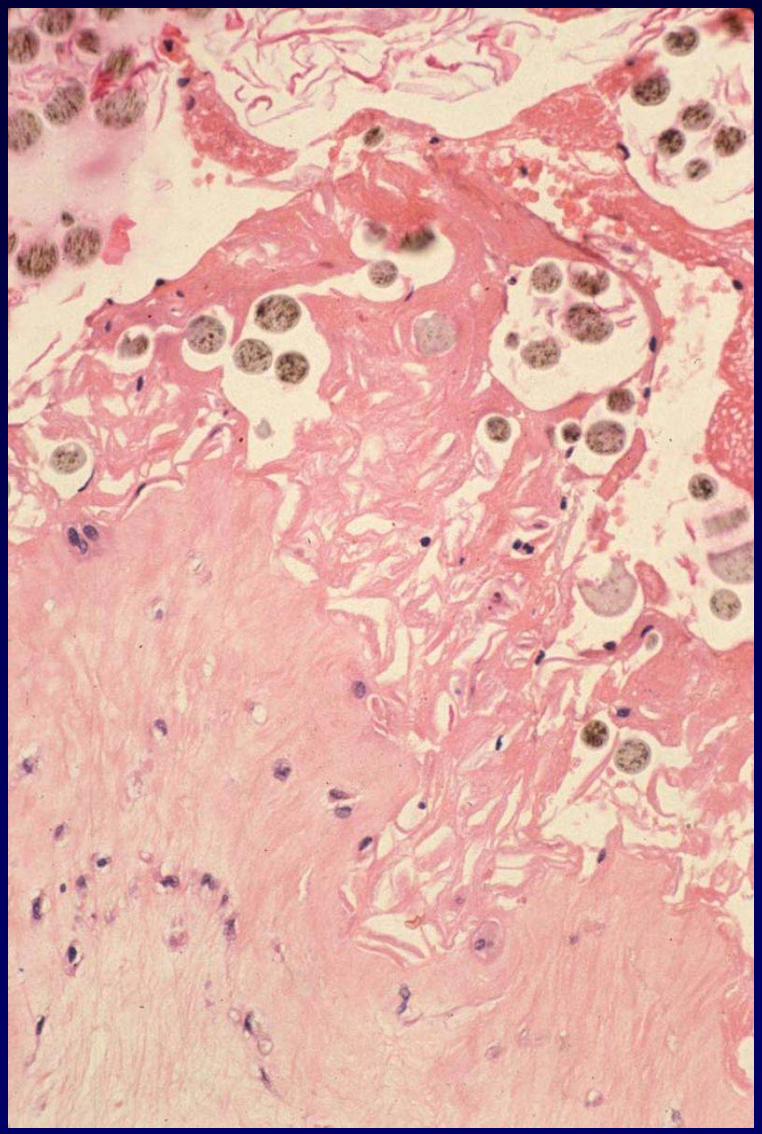


Nodule of squamous cells, hair and vernix caseosum material

Amnion Nodosum



Amnion Nodosum

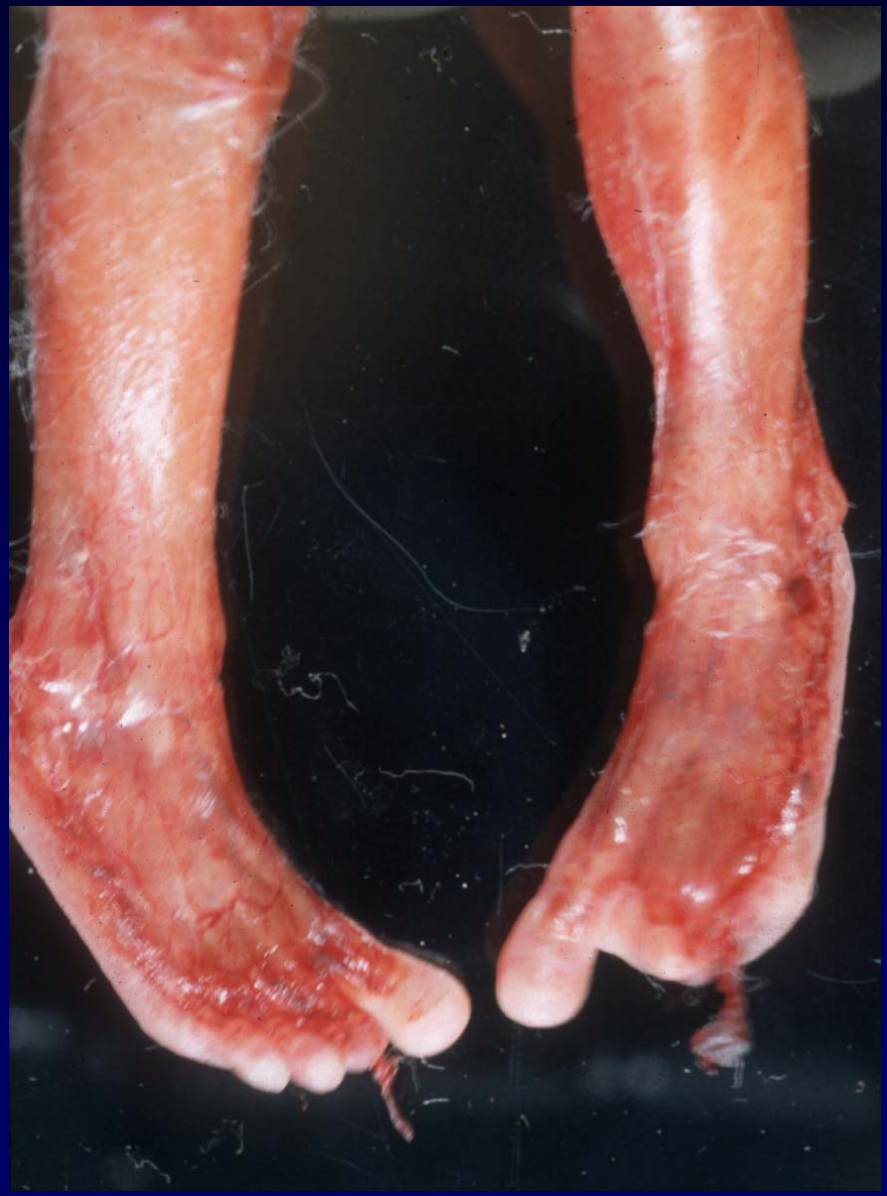


Amniotic Band Syndrome

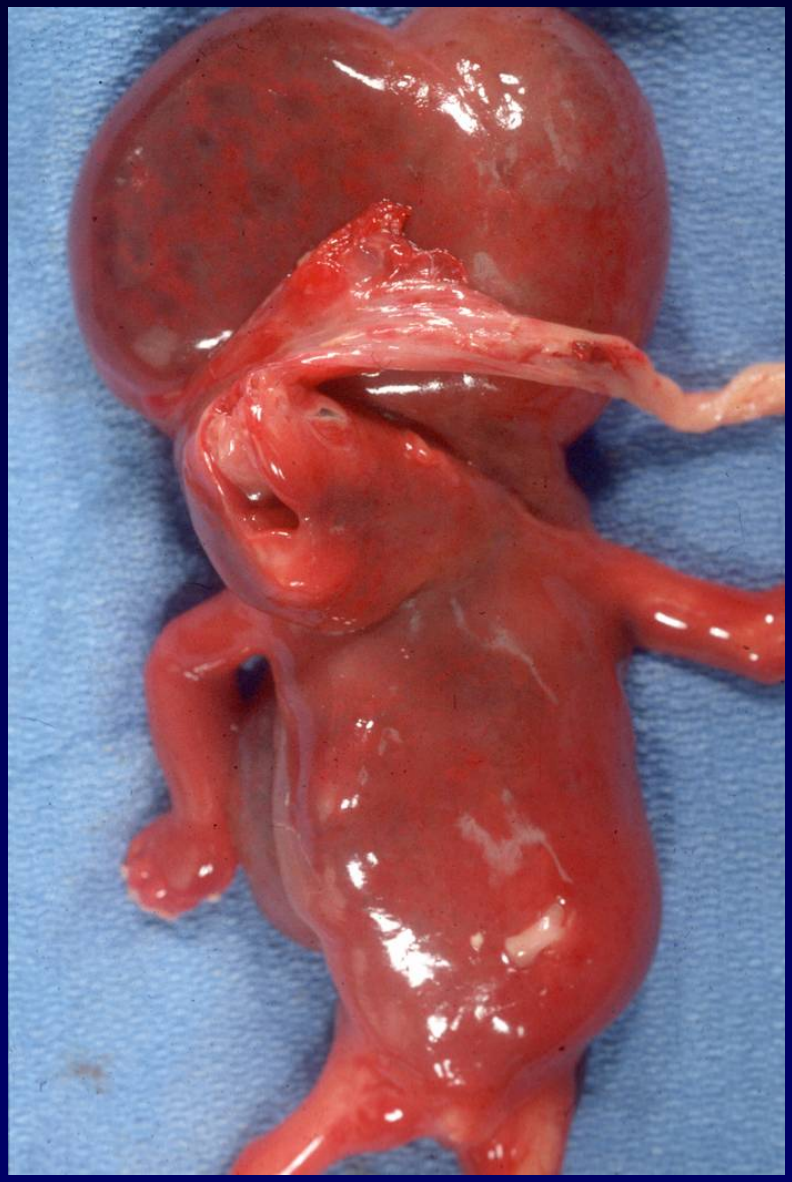
- Numerous other names
- Variable defects of limbs, trunk, craniofacial structures
- Malformations and deformations

Amniotic Band Syndrome

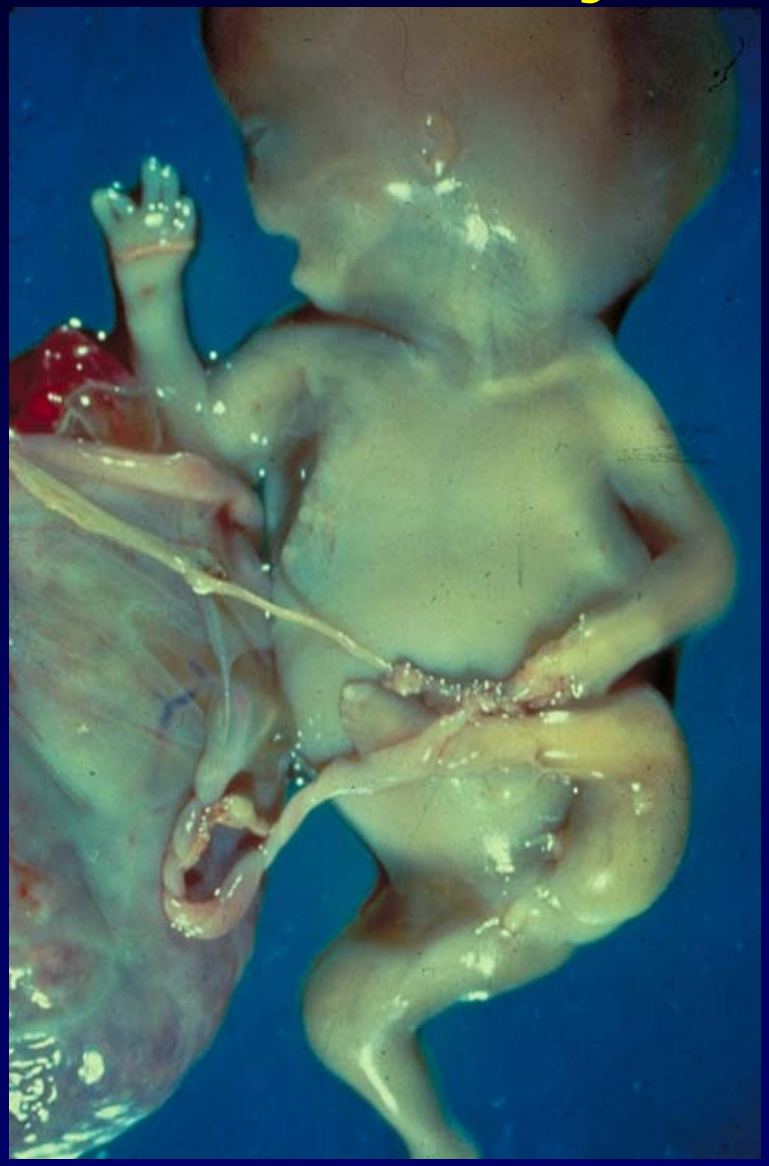
Amniotic Band Syndrome



Amniotic Band Syndrome

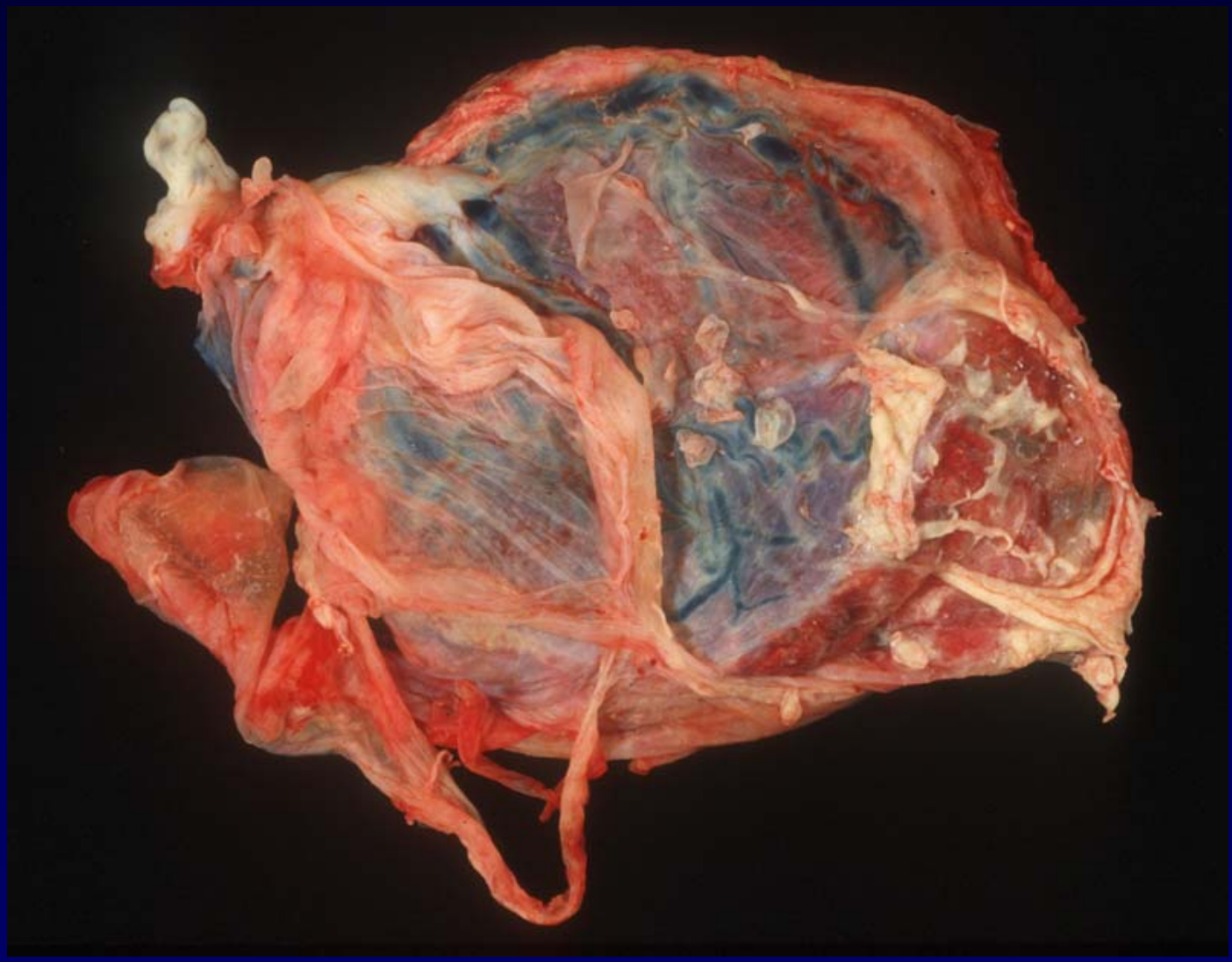


Amniotic Band Syndrome

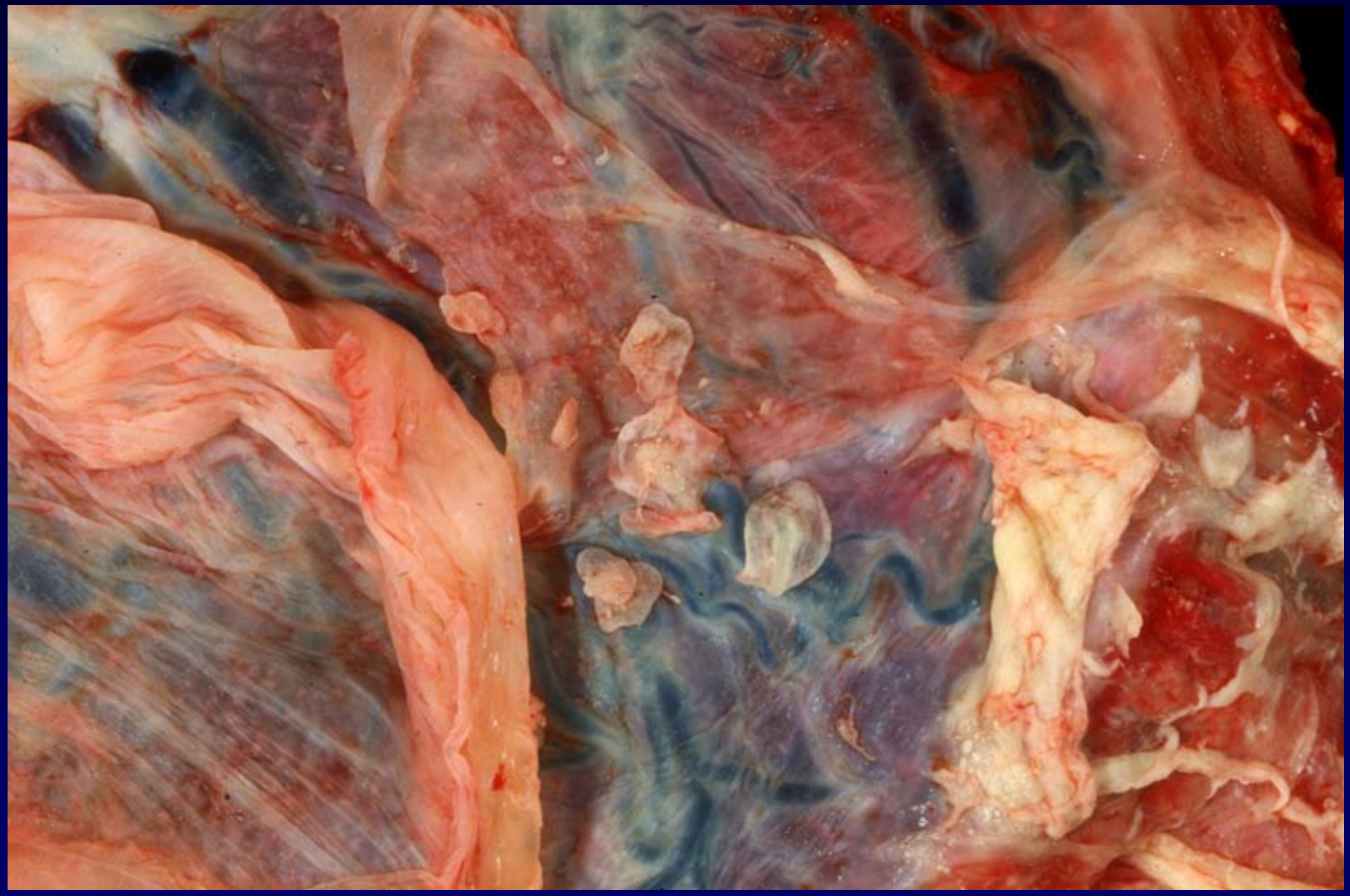


Amnionic Bands

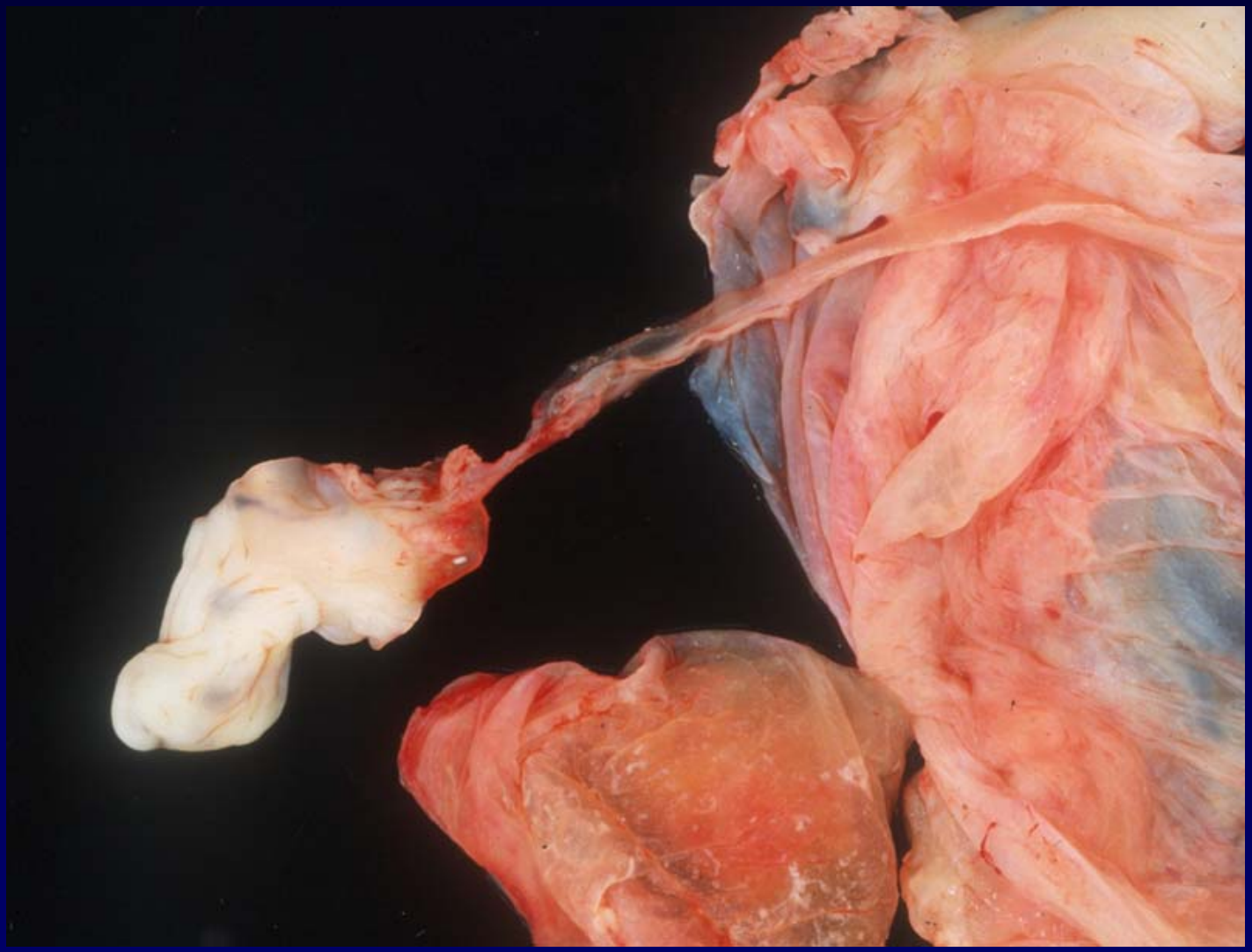
Amniotic Band Syndrome



Amniotic Band Syndrome

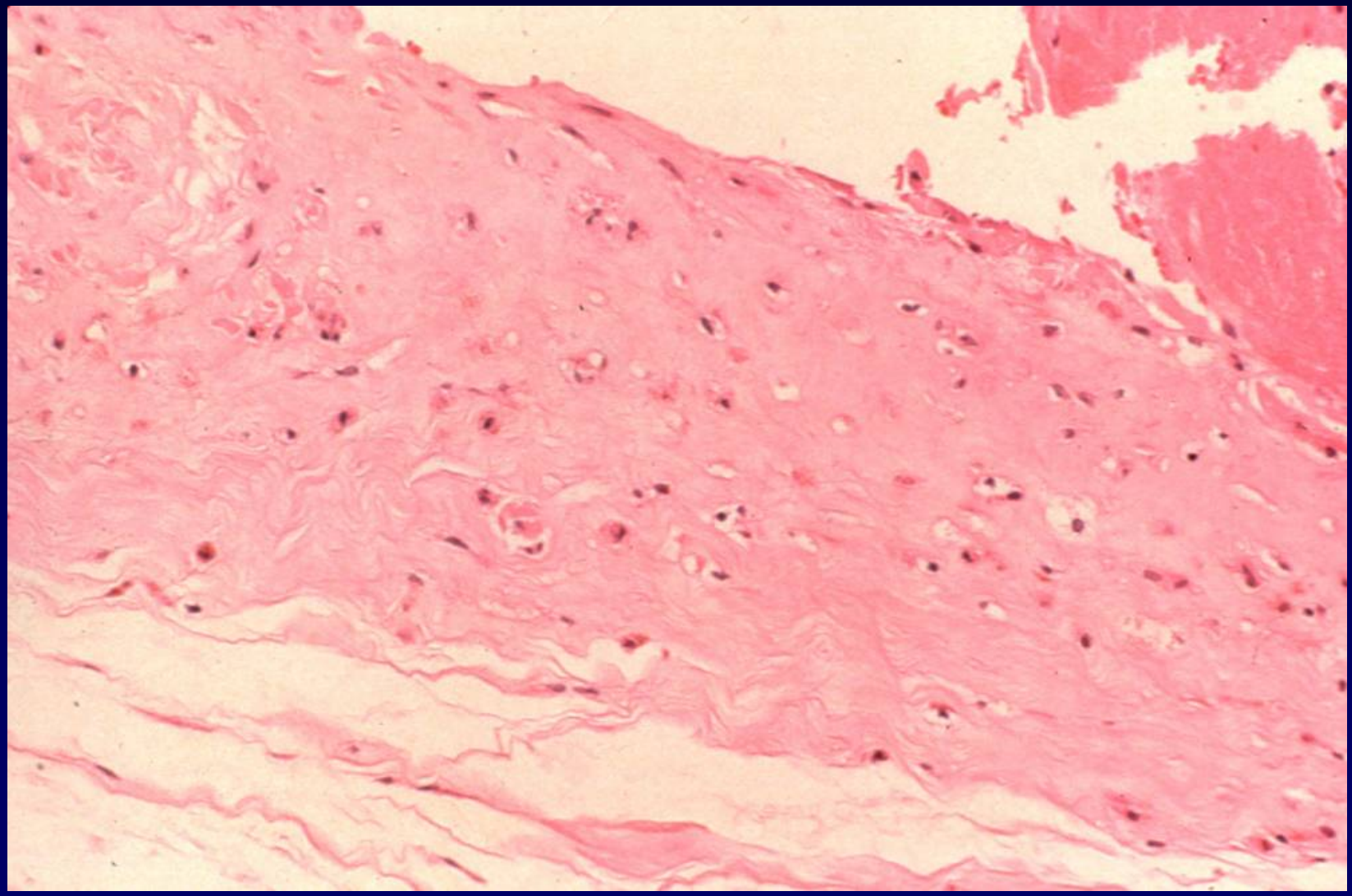


Amniotic Band Syndrome



Amniotic Band Syndrome

Amniotic Band Syndrome



Amniotic Band Syndrome

- 1:2500 to 1:8620 liveborns
- 1:55 previable fetuses
- Black multigravid women < age 20 years
- Often misdiagnosed as an hereditary syndrome

Amniotic Band Syndrome

Theories of pathogenesis:

- Amniotic bands cause defects
  - Timing of rupture determines severity
- Primary defect in embryo
- Vascular disruption

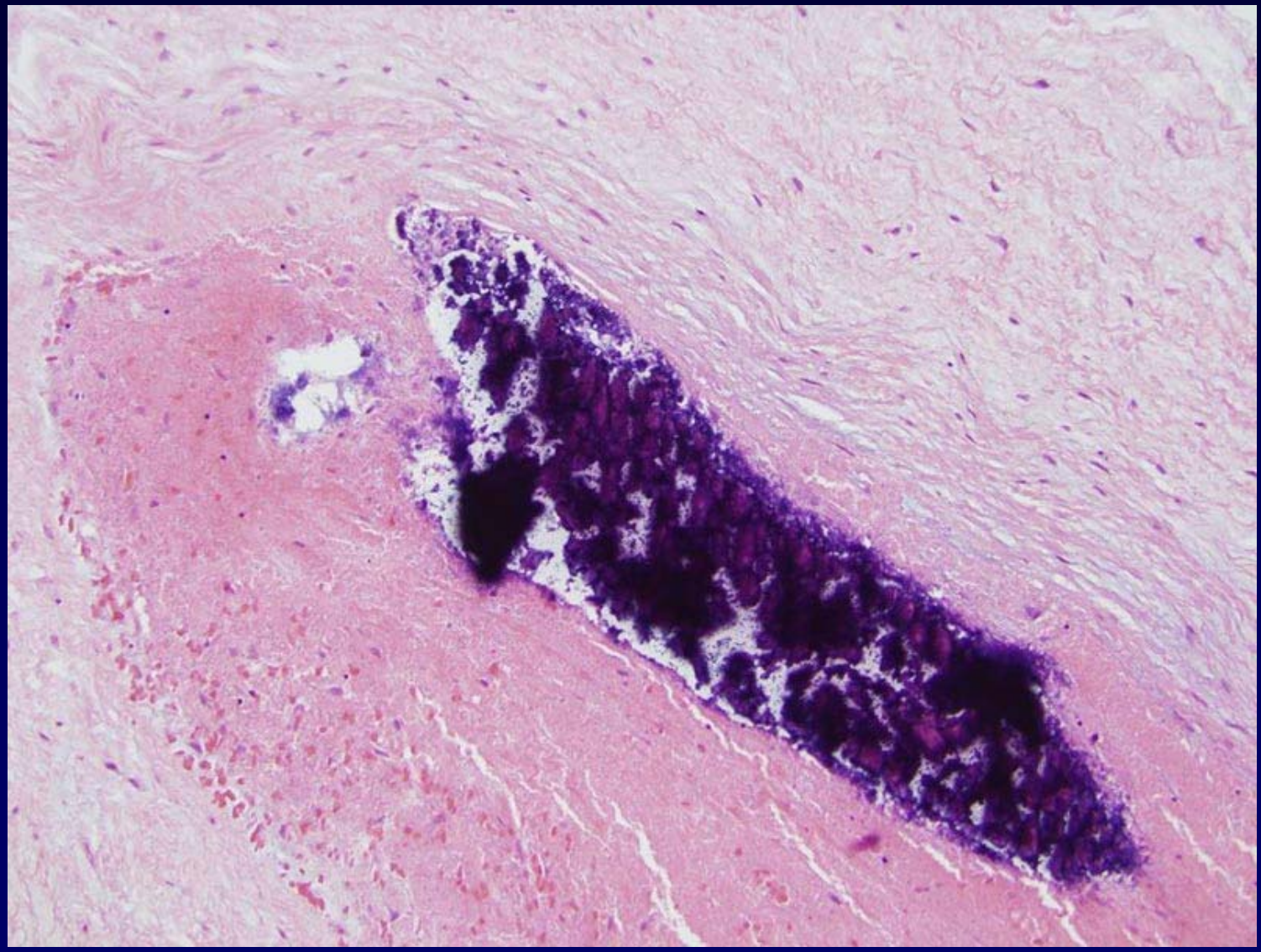
Amniotic Band Syndrome

- High index of suspicion
- Normal karyotype
- Recurrence is extremely rare

Case 9

The patient is a 35 year old woman with an intrauterine pregnancy at 33 weeks gestational age complicated by pregnancy-induced hypertension and premature rupture of membranes.

Umbilical Cord Thrombus



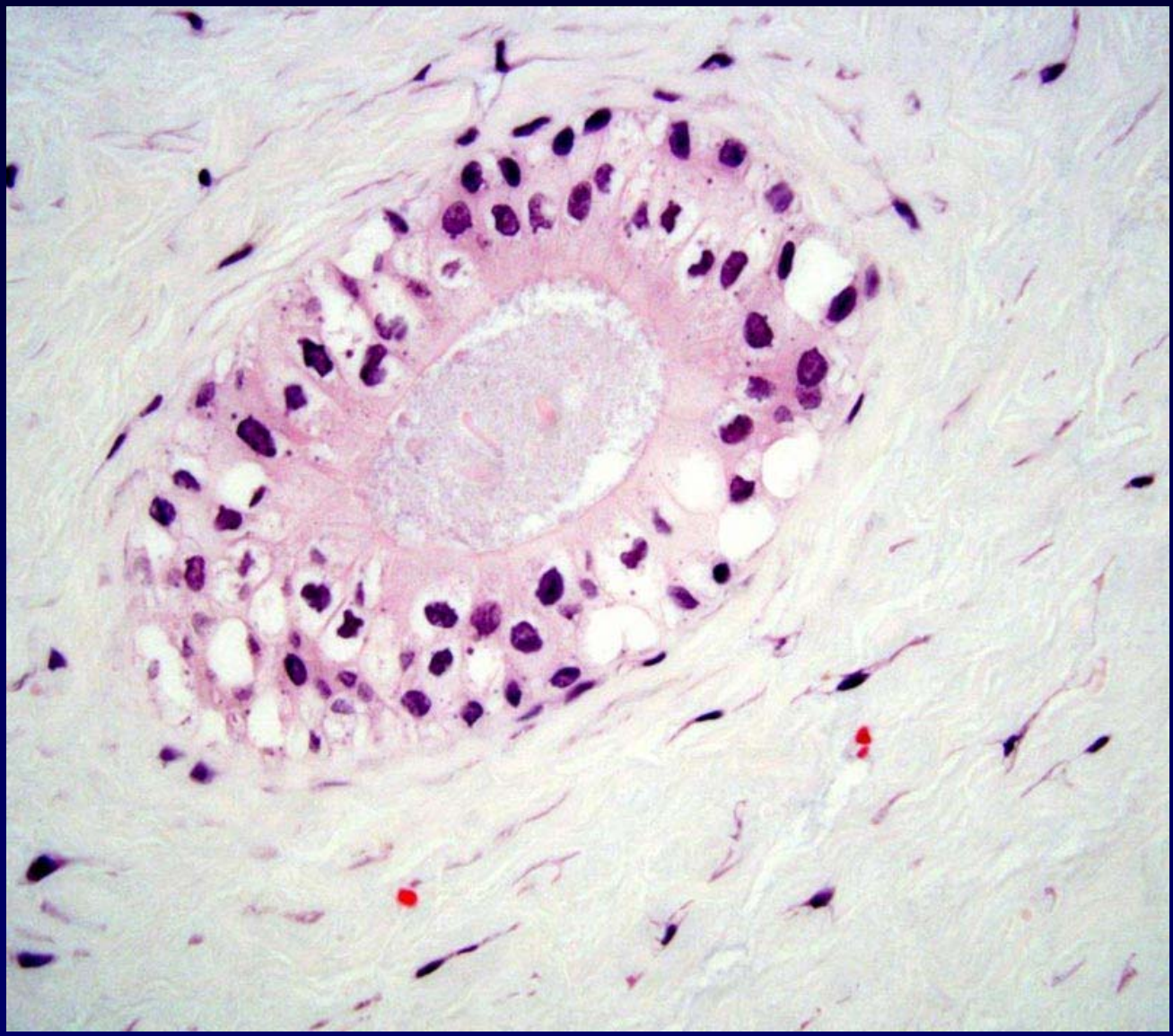
Umbilical Cord Thrombus

- 1:250 to 1:1500
- Vessel involved
  - Vein only - 71%
  - Vein and artery - 18%
  - Artery only - 11%
- Outcome
  - stillbirth - 2/3
  - neonatal distress or death -1/3

Embryonic Remnants

- Fusion of omphalomesenteric and allantoic ducts
- Ducts obliterated by end of 1st trimester
- Remnants found in 23%
- More than one remnant in 13%

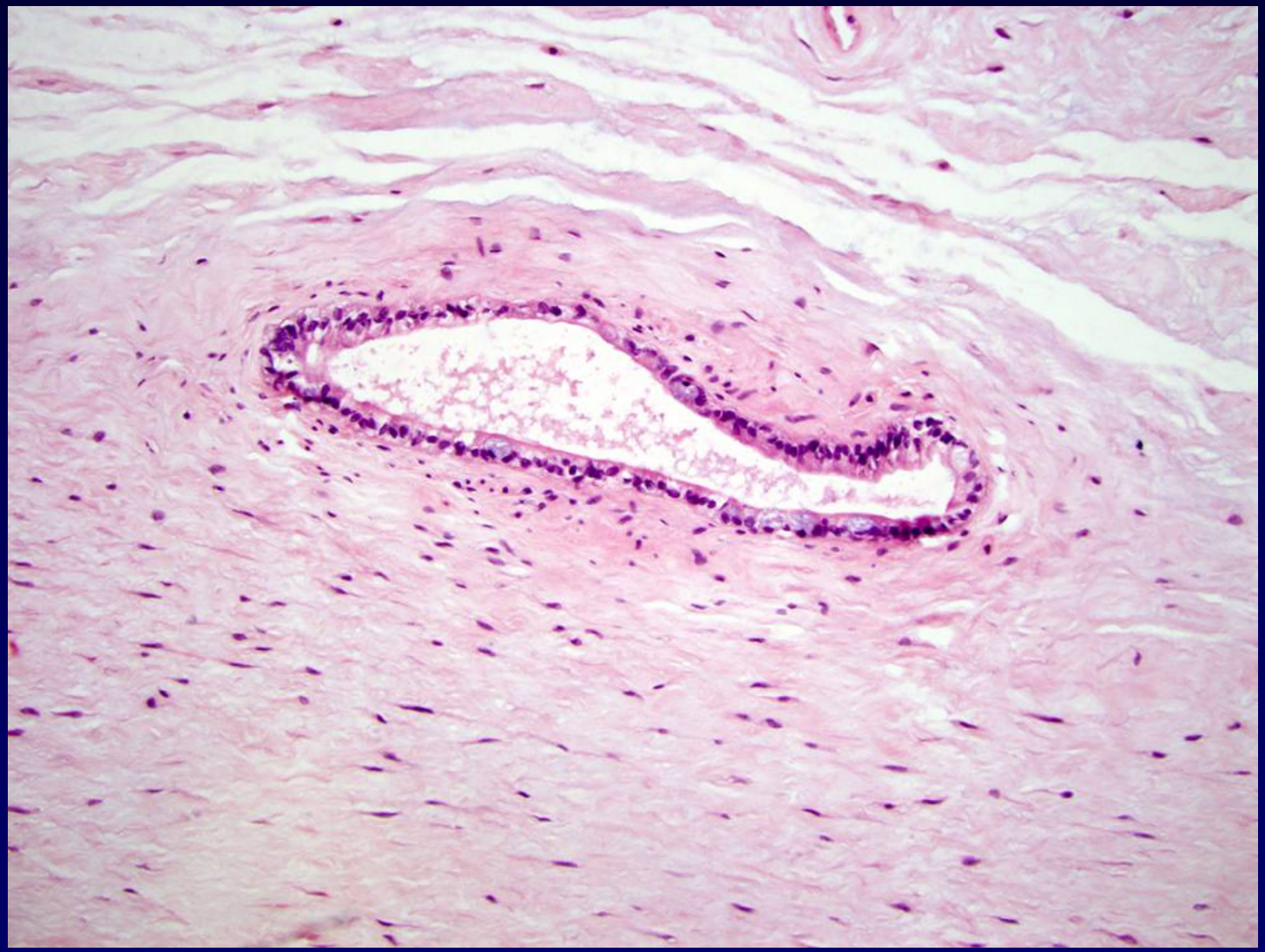
Allantoic Duct Remnant



Allantoic Duct Remnants

- Most common remnant
- Located between arteries
- Most common at fetal end of the cord
- Transitional-type epithelium
- Rarely form cysts
  - Associated with patent urachus

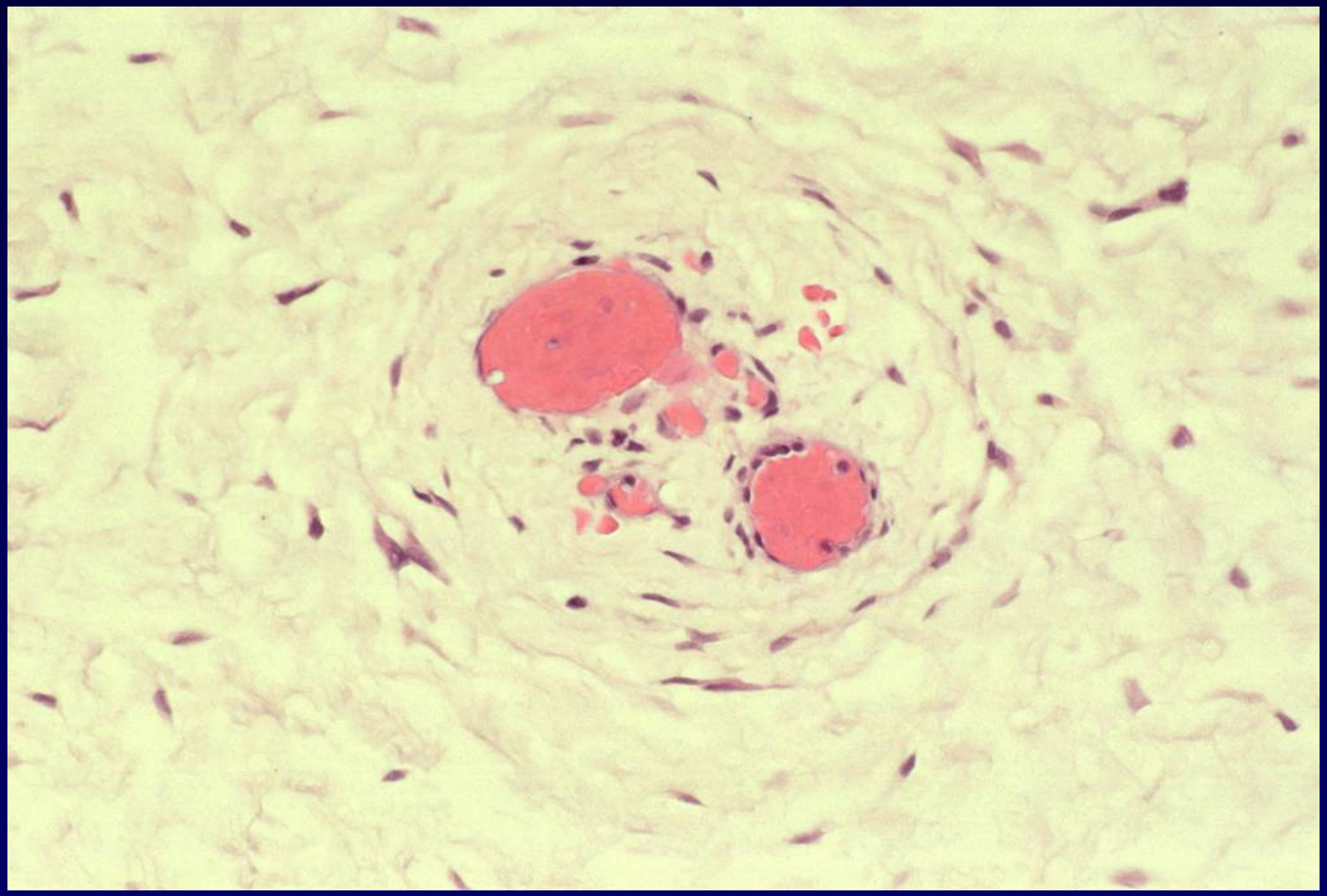
Omphalomesenteric Duct Remnants



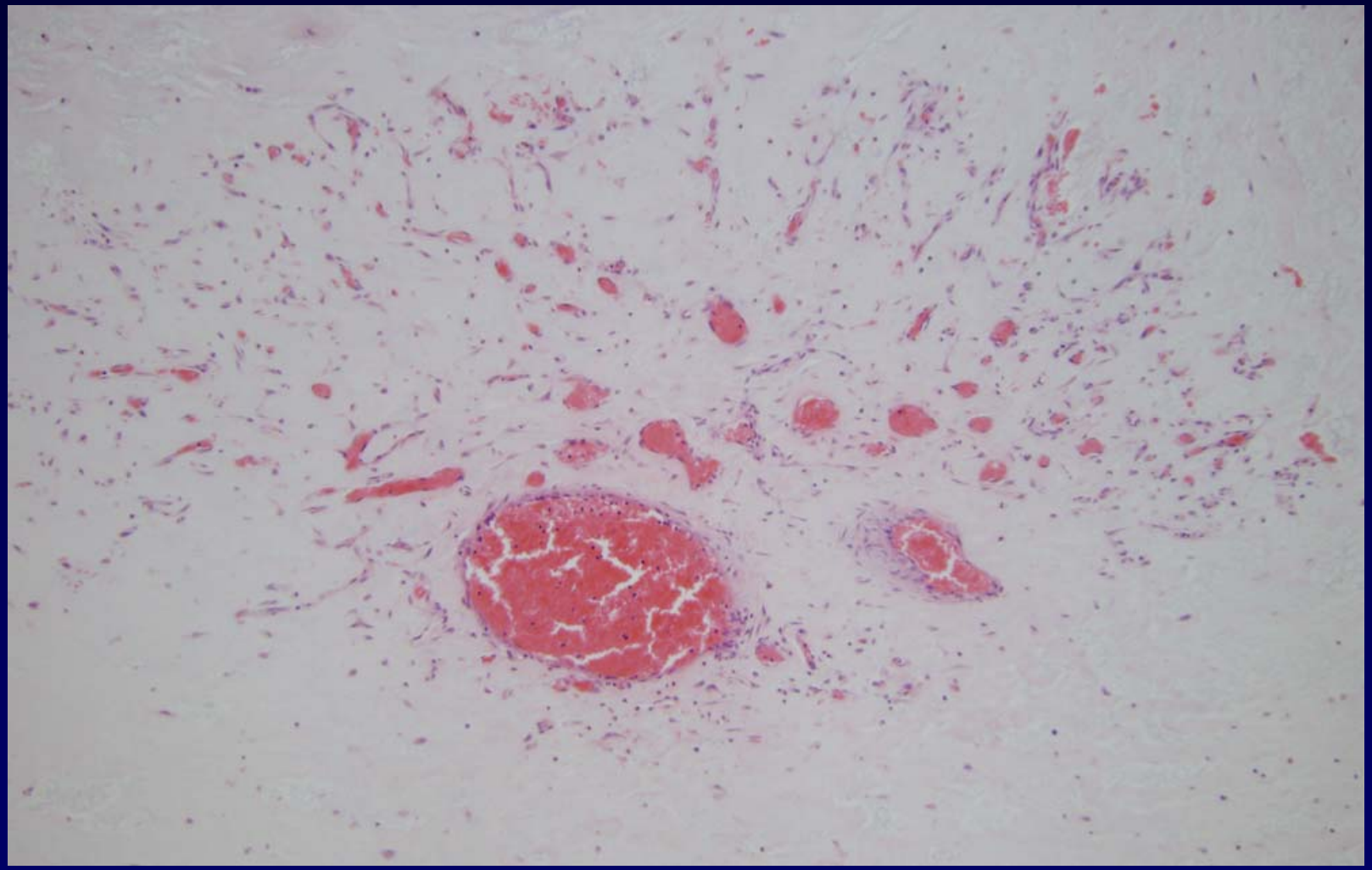
Omphalomesenteric Duct Remnants

- Located at cord margin
- Most common at fetal end
- Cuboidal or columnar epithelium
- May see smooth muscle, gastric, pancreatic differentiation
- Cysts are rare, associated with Meckel's

Vitelline Vessel Remnants

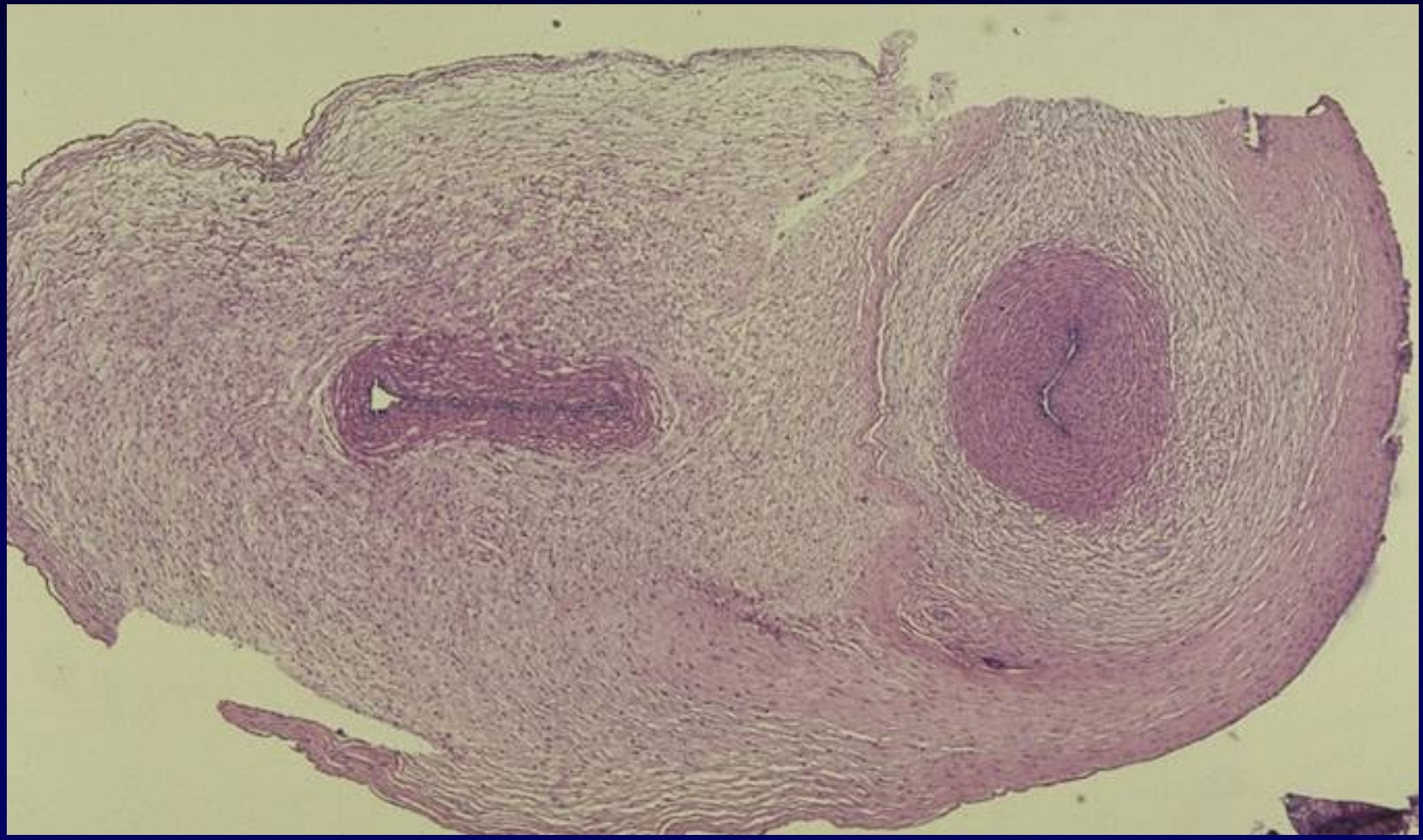


Vitelline Vessel Remnants



Located at periphery, most common at fetal end

Single Umbilical Artery



Single Umbilical Artery

- See in 1% of umbilical cords
- Highest in eastern Europeans
- 3 to 4-fold increase in twins vs. singletons
- Fixed gross or micro finds more SUA
- Umbilical arteries fuse just before disk

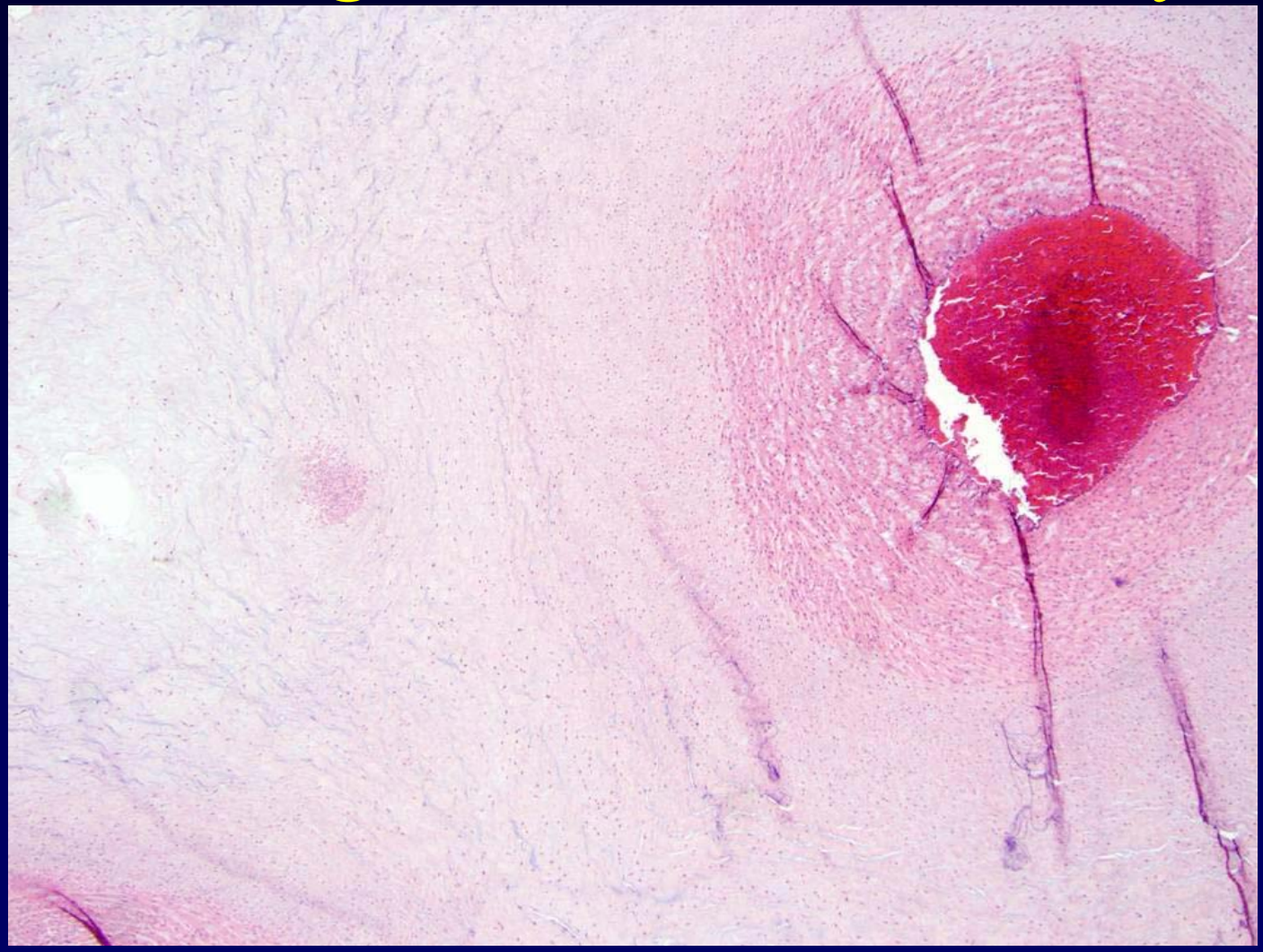
Single Umbilical Artery

- Increase in major malformations
  - 21% - 7 fold higher than controls
  - No pattern to malformations
- Increase in mortality
  - 20% - 5 fold higher than controls
  - Most deaths due to malformations
  - Associated with low birth weight and growth restriction

Single Umbilical Artery

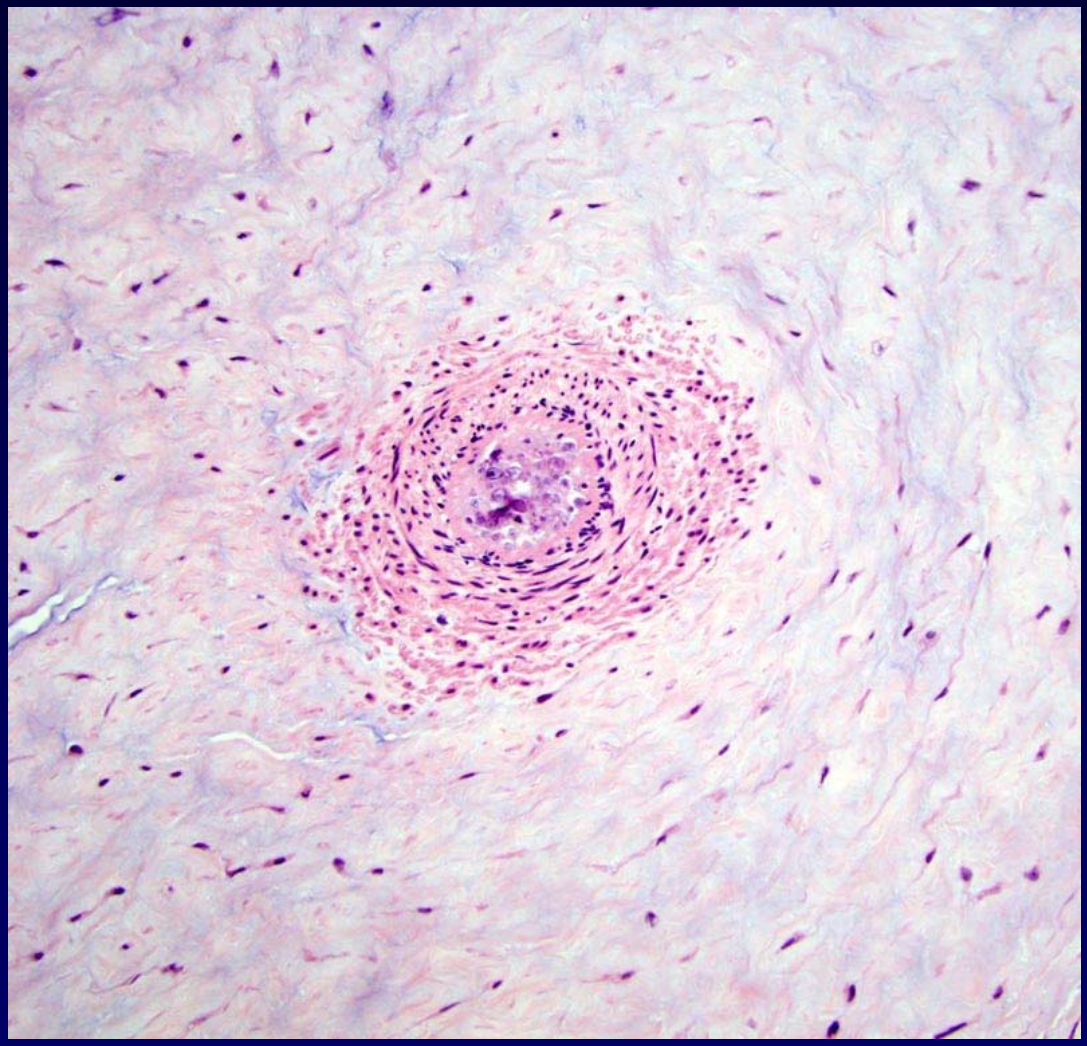
- May play a role in congenital anomalies
- Decreased flow to placenta may increase fetal cardiac workload
- Decreased flow to tissues could cause chronic hypoxia
- Smaller twin usually has SUA

Single Umbilical Artery



Atrophic remnant of other umbilical artery

Single Umbilical Artery



Atrophic remnant of second umbilical artery

Single Umbilical Artery

Associated placental abnormalities

- Velamentous cord insertion - 9.3% (con=1.2%)
- Marginal cord insertion – 18% (con=5.9%)
- Extrachorialis
- Bilobation
- Succenturiate lobe
- Placenta previa
- Chorangiomas
- Increased infarction

Single Umbilical Artery

Maternal associations

- Age, gravidity, prior loss - no relationship
- Diabetes, HTN, toxemia - controversial

Outcome

- External anomalies - ↑ risk of internal anomalies
- No external anomalies, no sx – work up unclear
- No anomalies, +IUGR - will catch up

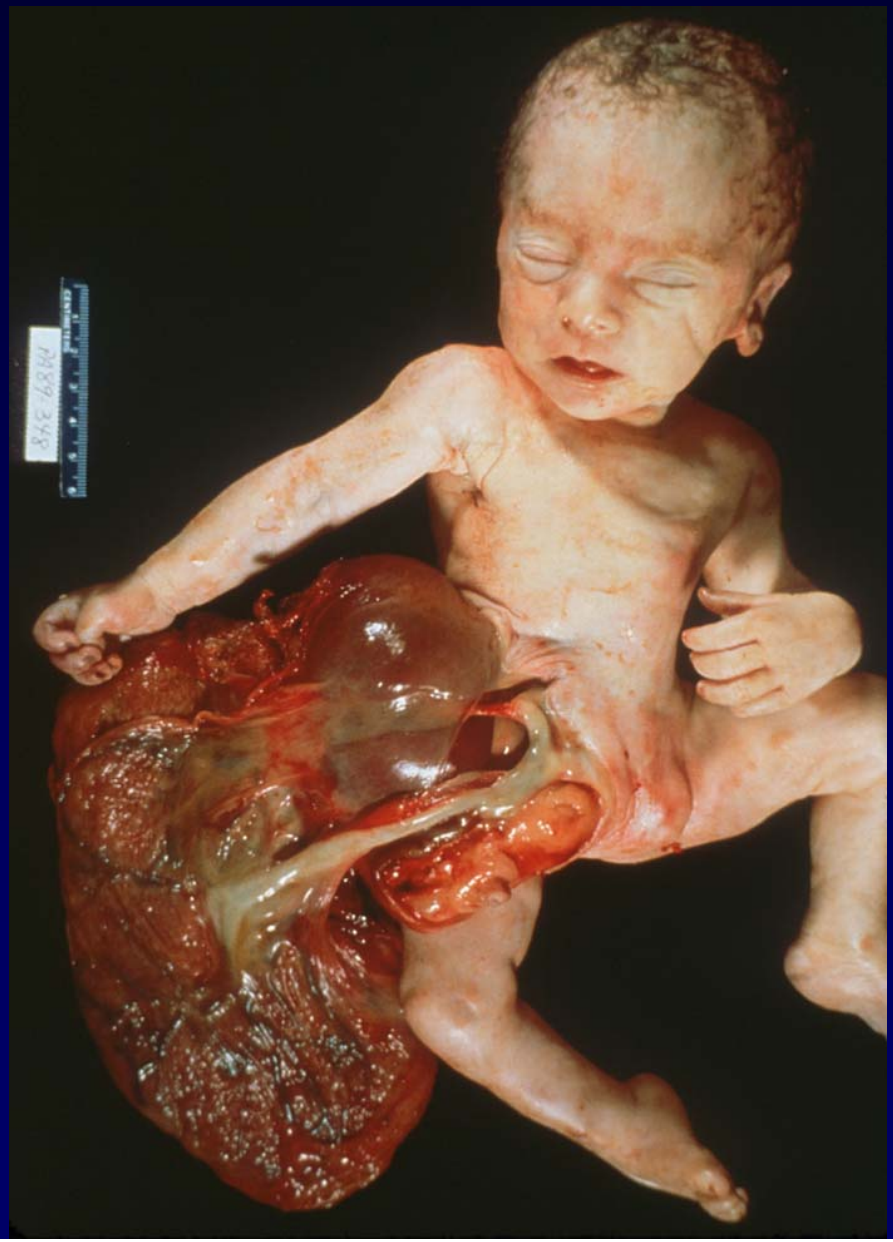
Umbilical Cord Length

- Mean length - 55 to 60 cm
- Related to tension
- Maternal height and weight is controversial

Short Umbilical Cord

- < 40 cm
- See in 6% of cases
- Associated with ↓ fetal movements:
  - Amniotic bands, arthrogryposis, oligohydramnios, body wall defects, fetal neuromuscular disorders

Short Umbilical Cord



Short Umbilical Cord

- Post natal associations:
  - Low Apgar scores
  - Jitters and trembles
  - Hypotonia
  - Need for positive pressure resuscitation
  - Psychomotor abnormalities

Long Umbilical Cord

- > 80 cm
- See in 6% of cases
- Increased risk of
  - Nuchal cord
  - Other encirclement
  - Cord prolapse
  - Marked twisting

Long Umbilical Cord

- Significant association between long cords and placental abnormalities
  - ↑ nucleated RBCs
  - Chorangiosis
  - Fetal vascular thrombi
  - Meconium macrophages

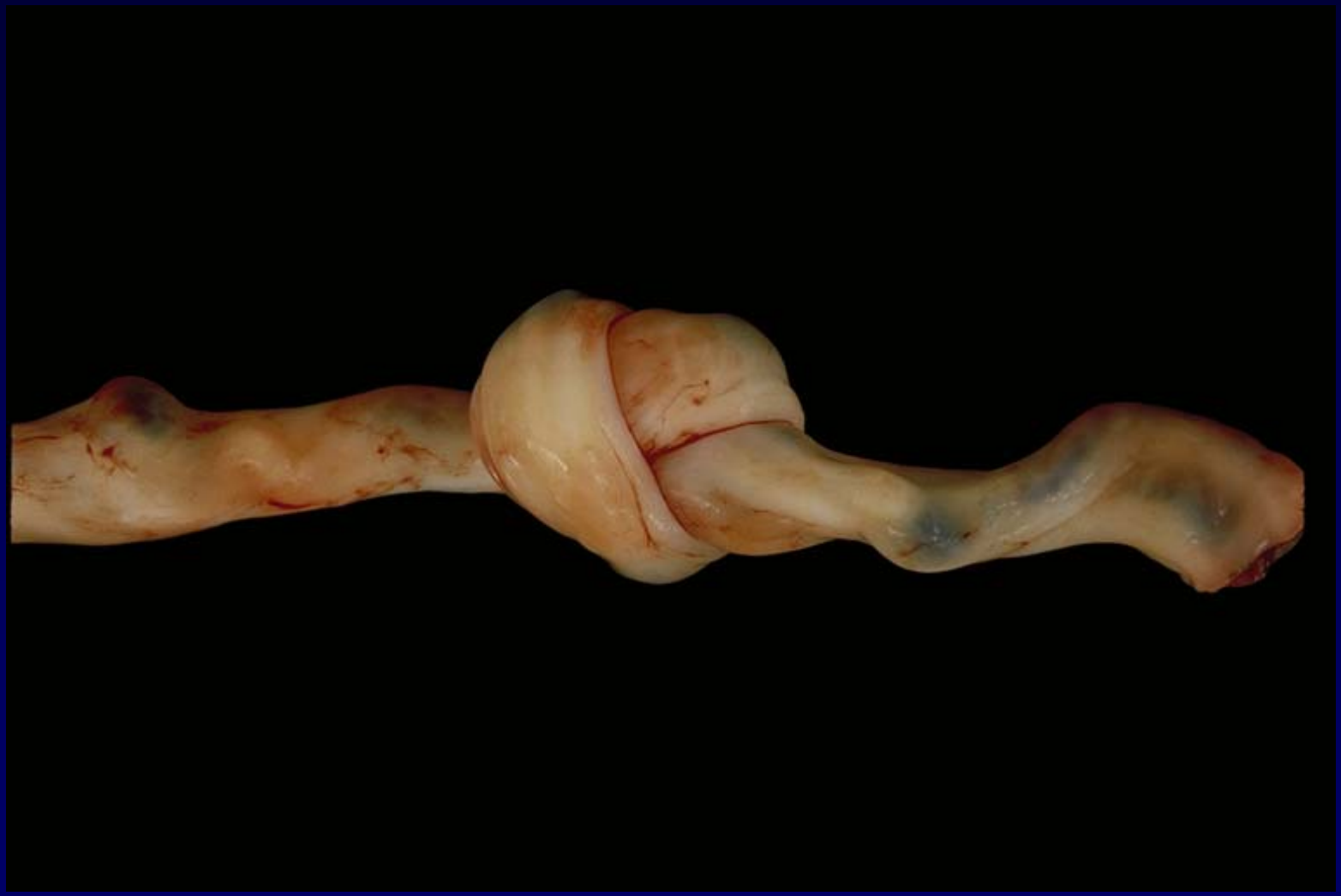
Long Umbilical Cord

If >90 cm half had:

- Abnormal CNS imaging
- Neurologic abnormalities
- Both

May have long cord in subsequent pregnancy

Umbilical Cord Knot



Umbilical Cord Knots

- See in 1% of cords
- Develop between 9 and 12 weeks
- Mortality between 5 and 11%

Umbilical Cord Knots

Acute tightening

- Edema, congestion, thrombi on one side
- Collapse between knot and fetus

Chronic tightening

- Untie and see persistent groove, loss of Wharton's jelly, curving

Umbilical Cord Knots

Clinical associations

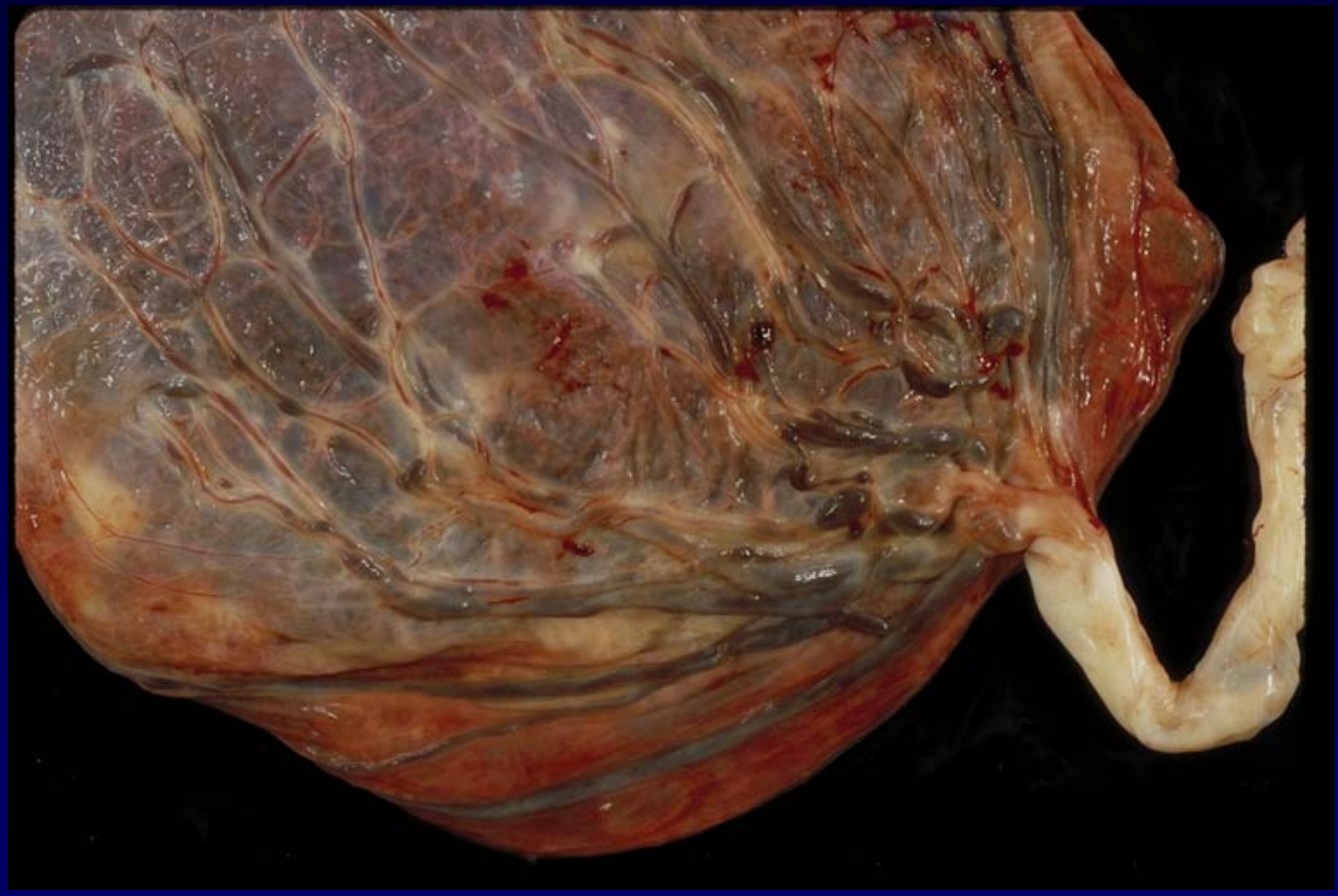
Long cords
Male gender
Multiparity
hydramnios

Diabetes
Growth retardation
Genetic amniocentesis
Monoamniotic twins

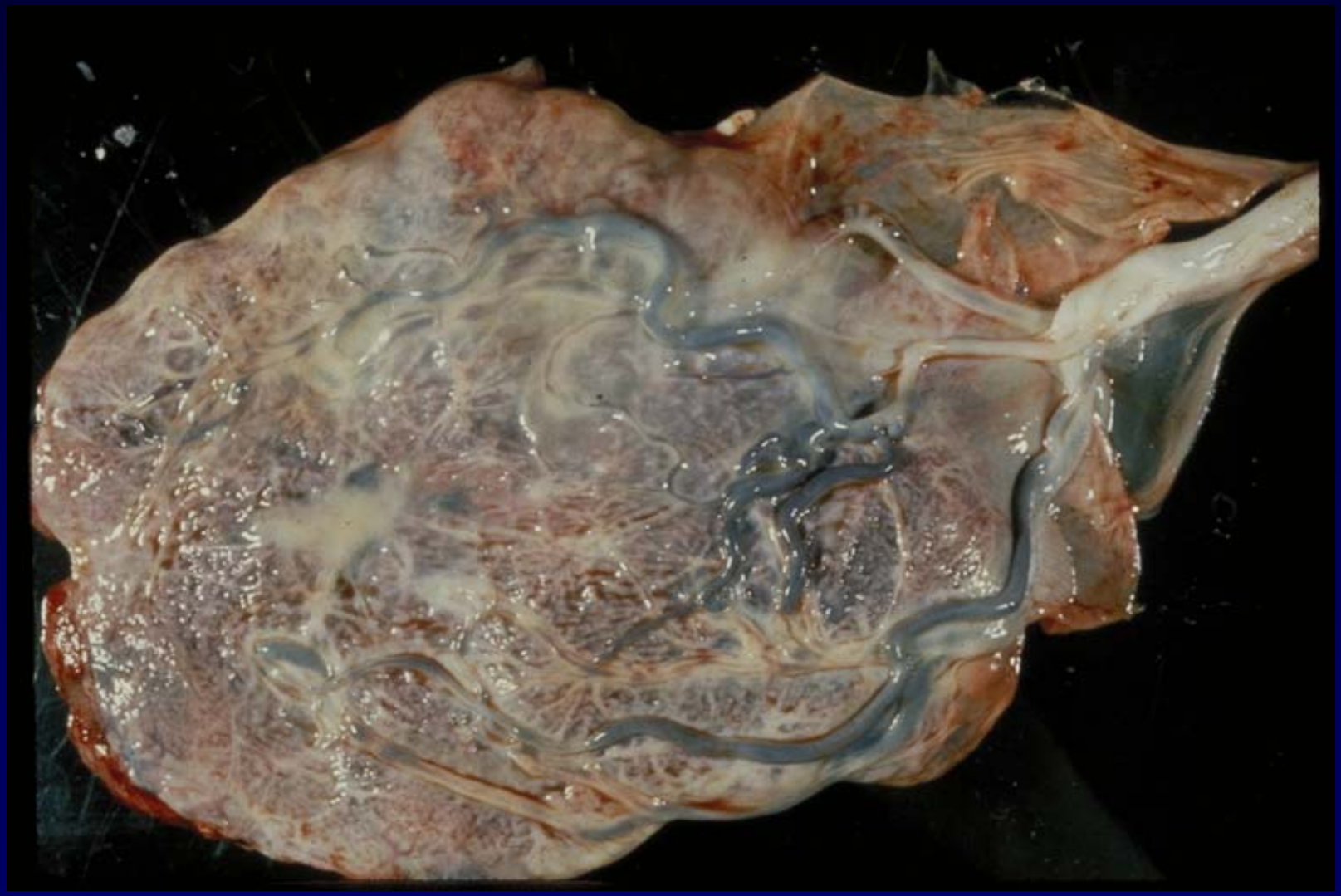
Abnormal Cord Insertion

- Marginal - 5.9 to 18%
- Velamentous - 1%
  - Insertio velamentosa - 75% branch in membranes
  - Interposition velamentosa - 25% don’t branch
- Insertio furcata
  - Don’t insert in membranes but do branch

Marginal Insertion



Velamentous Insertion



Sample intramembranous vessels (do a roll)

Velamentous Cord Insertion

Clinical associations:

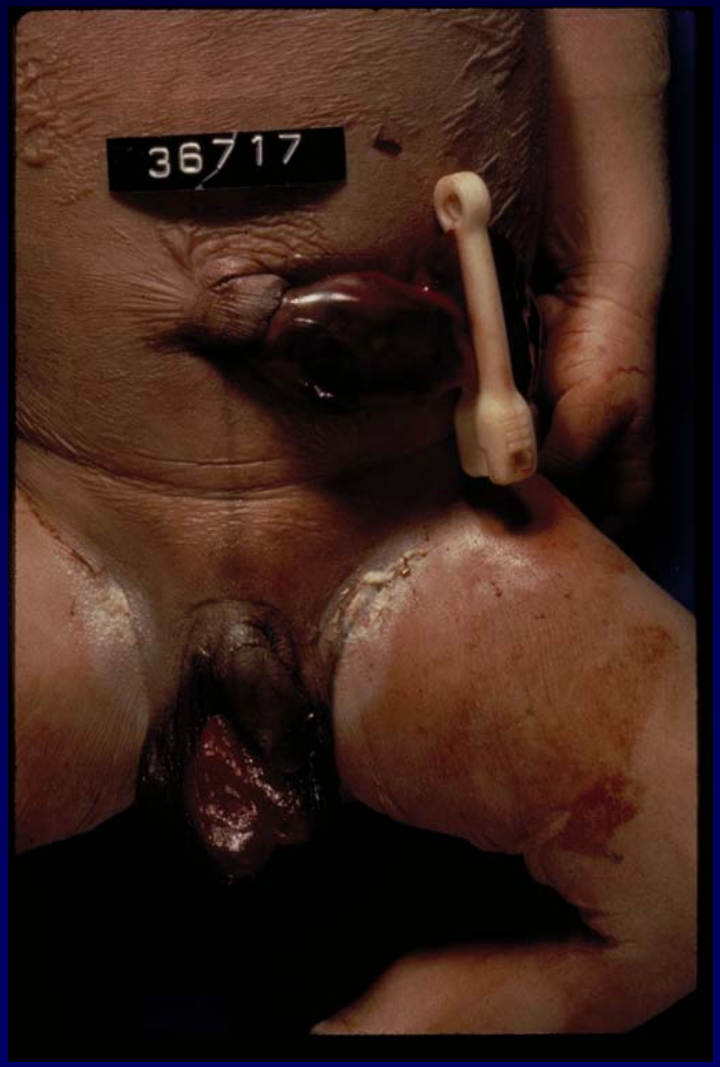
- Twins 8.5%
  - Monochorionic > fused dichorionic > separate dichorionic
- Single umbilical artery
- Congenital malformations
- IVF conception
- Maternal smoking, diabetes, advanced age

Velamentous Cord Insertion

Complications

- Laceration
- Compression and thrombosis
- Deformation anomalies
- Vasa previa - vessels over os
  - 1:50 velamentous insertions
  - Sudden exsanguination - high mortality

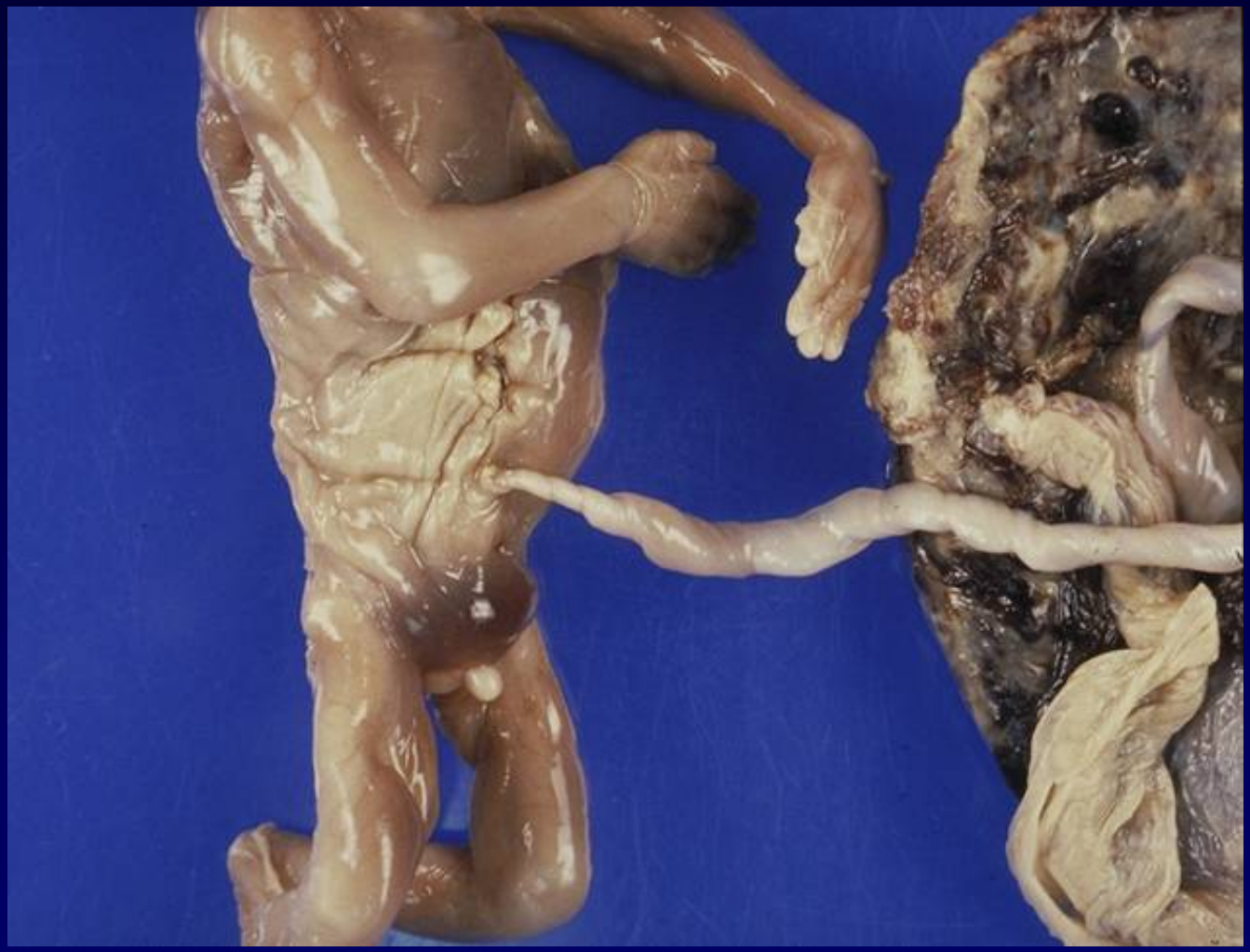
Umbilical Cord Hematoma



Umbilical Cord Hematoma

- 1:5500 deliveries
- 50% perinatal mortality rate
- Usually involves fetal end
- Causes
  - Trauma
    - See after 1.5% of US-guided cord sampling
    - Little morbidity or mortality
  - Inflammation
  - Primary vessel defect

Umbilical Cord Stricture



Umbilical Cord Constriction

- Uncommon
- High rate of stillbirth
- Early gestations
- Long cords, excess twisting

Umbilical Cord Constriction

Is it a postmortem artifact?

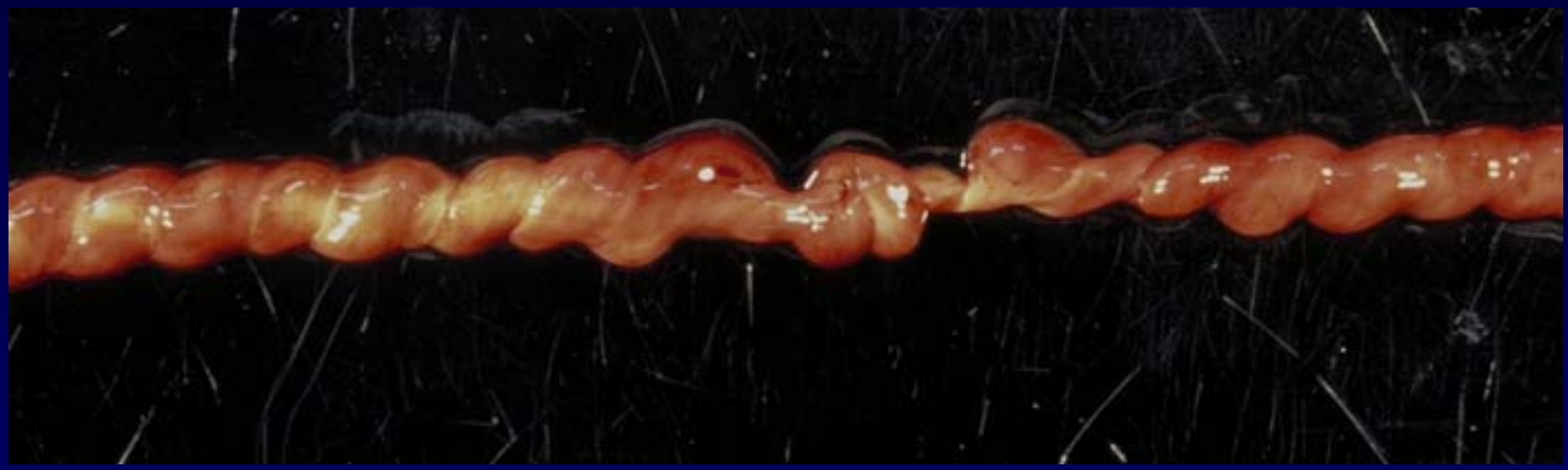
To attribute a fetal death to constriction

- Edema
- Venous congestion
- Occlusive thrombi

Umbilical Cord Spiral

- Average 10 turns
- Counter-clockwise
- Established early in gestation
- Function
  - ↑ turgor
  - ↓ compression
  - ↑ venous return

Excess Cord Torsion



Hypercoiled Cord

- Coiling index > 90th percentile
- Clinical associations
  - Fetal death
  - Preterm delivery
  - Low birth weight
  - Abnormal cord insertion
  - Maternal cocaine use
  - Extremes of maternal age

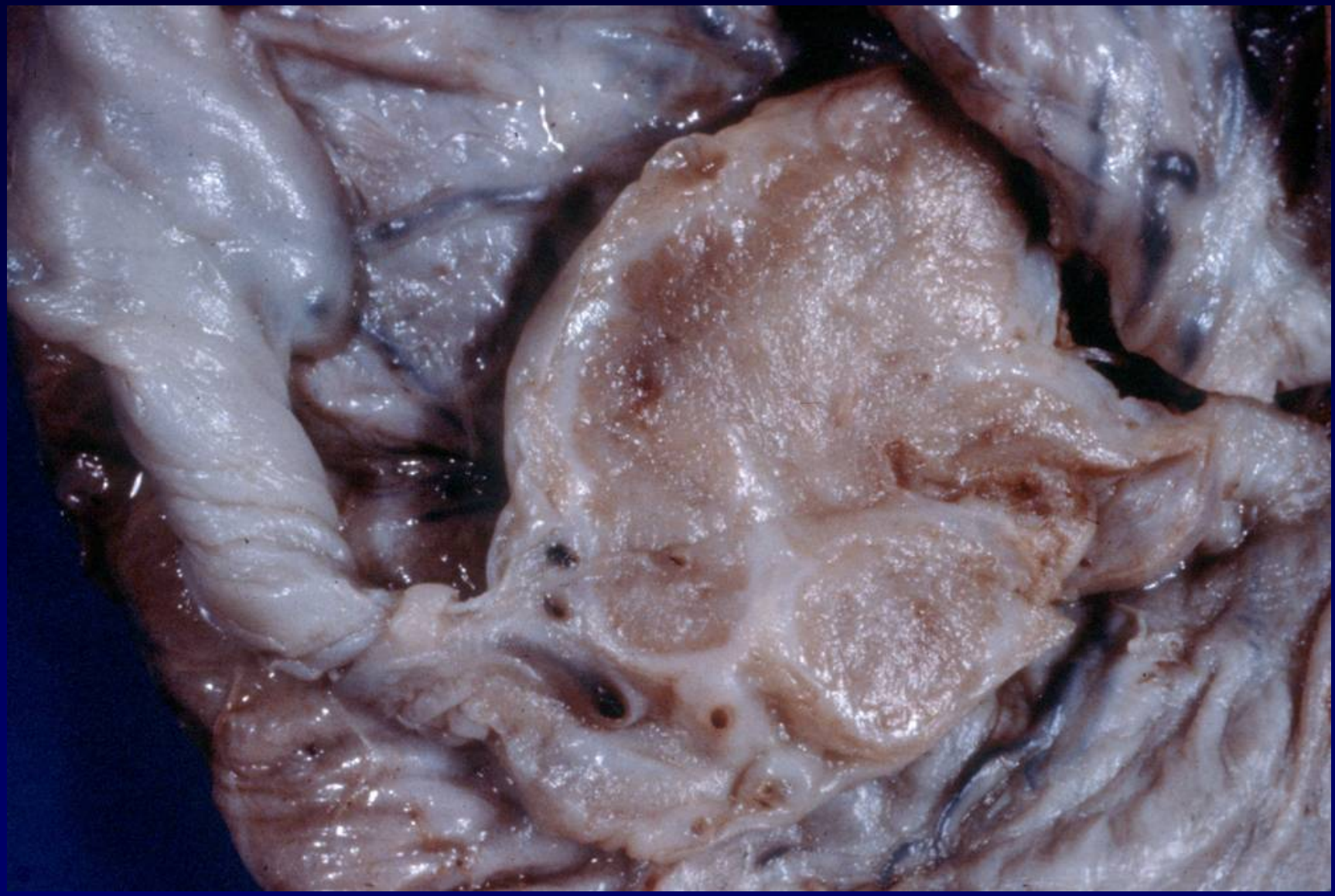
Uncoiled Cord

- 5% of cords
- Clinical associations
  - ↑ mortality
  - C-section for distress
  - Meconium
  - Preterm delivery
  - Abnormal karyotype
  - Abnormal heart tracing

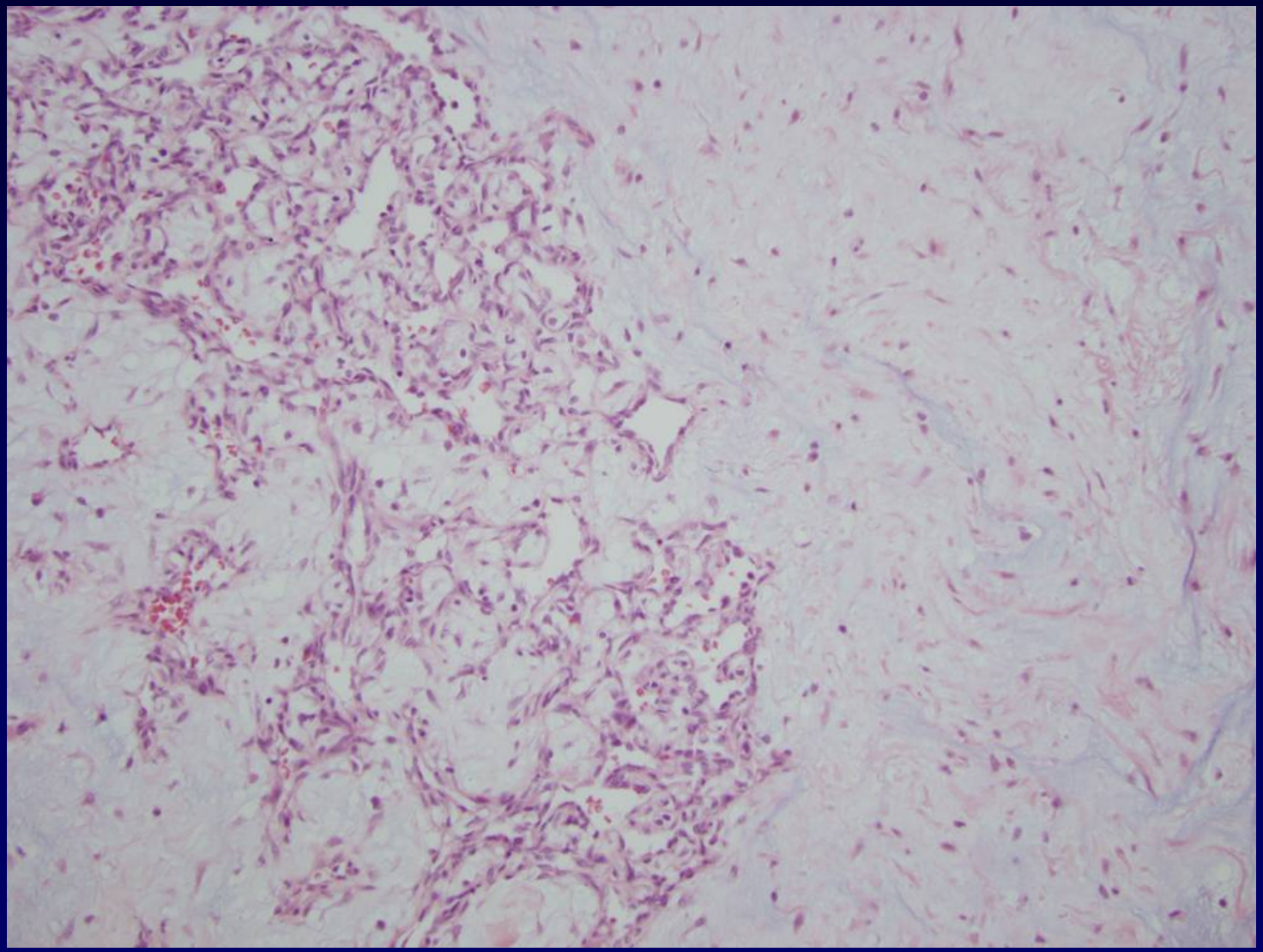
Hypocoiled Cord

- Coiling index < 10th percentile
- Clinical associations
  - Preterm delivery
  - Growth retardation
  - C-section for distress
  - Meconium, oligohydramnios
  - Abnormal karyotype
  - Nuchal cord

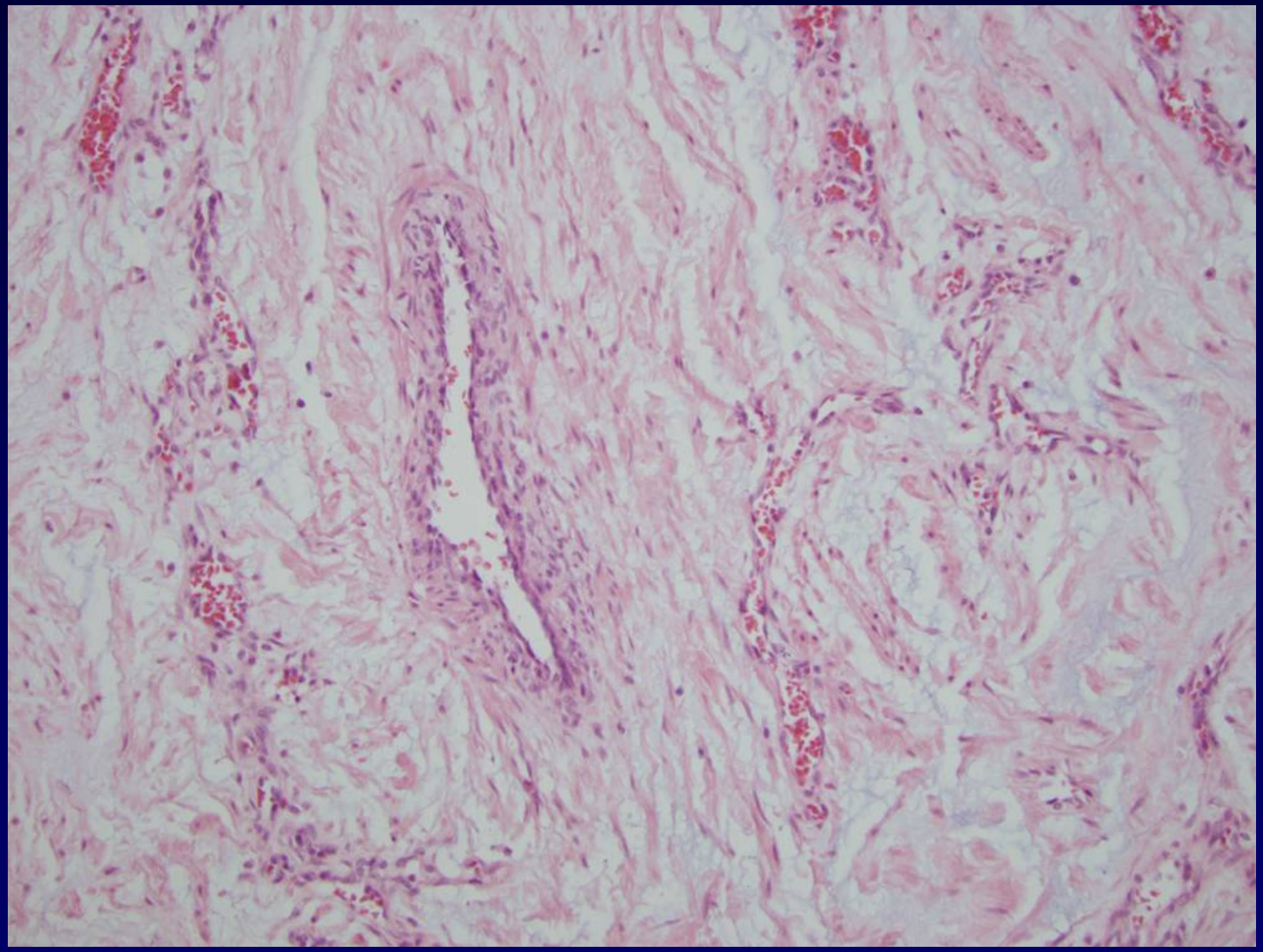
Umbilical Cord Hemangioma



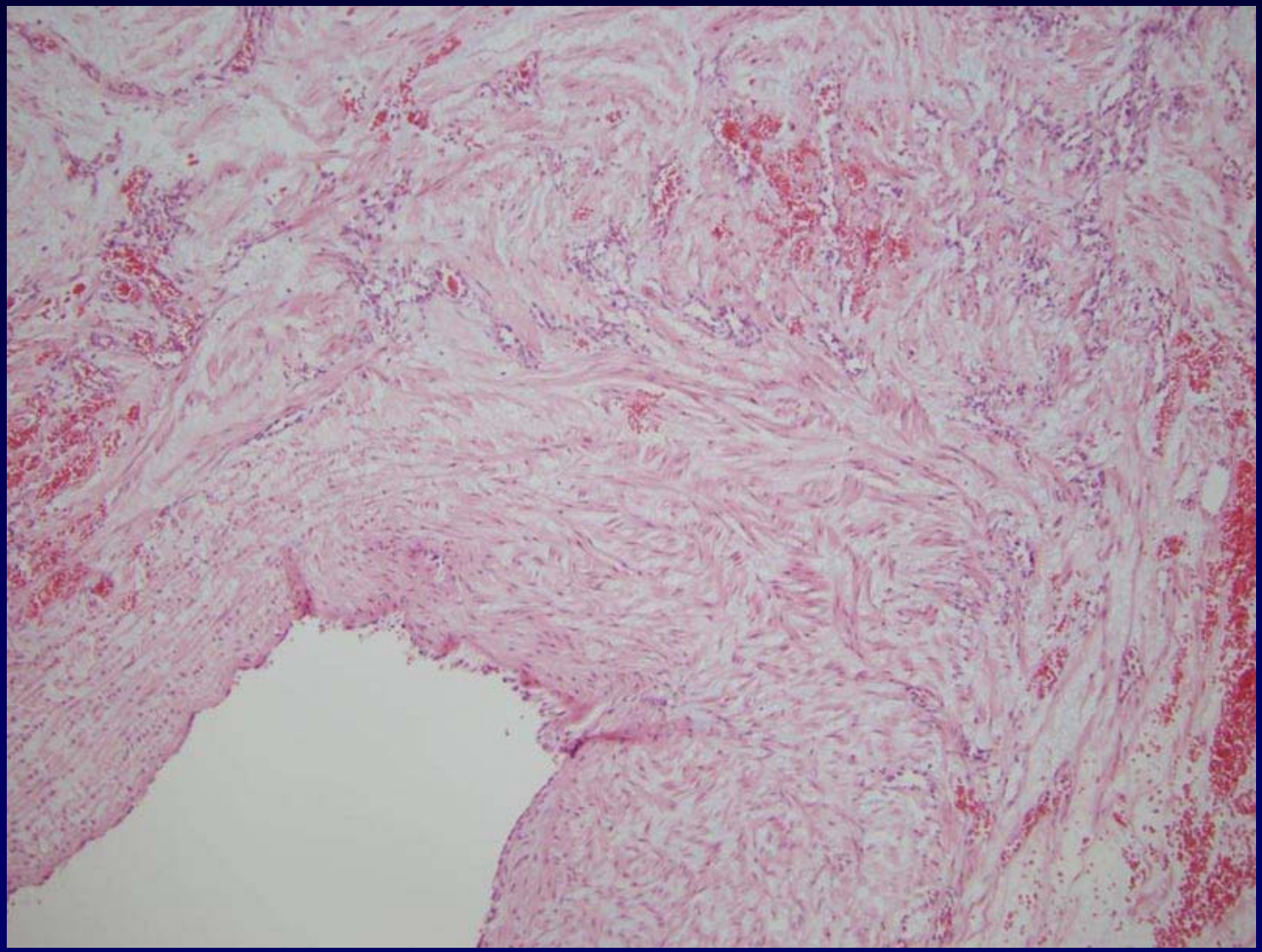
Umbilical Cord Hemangioma



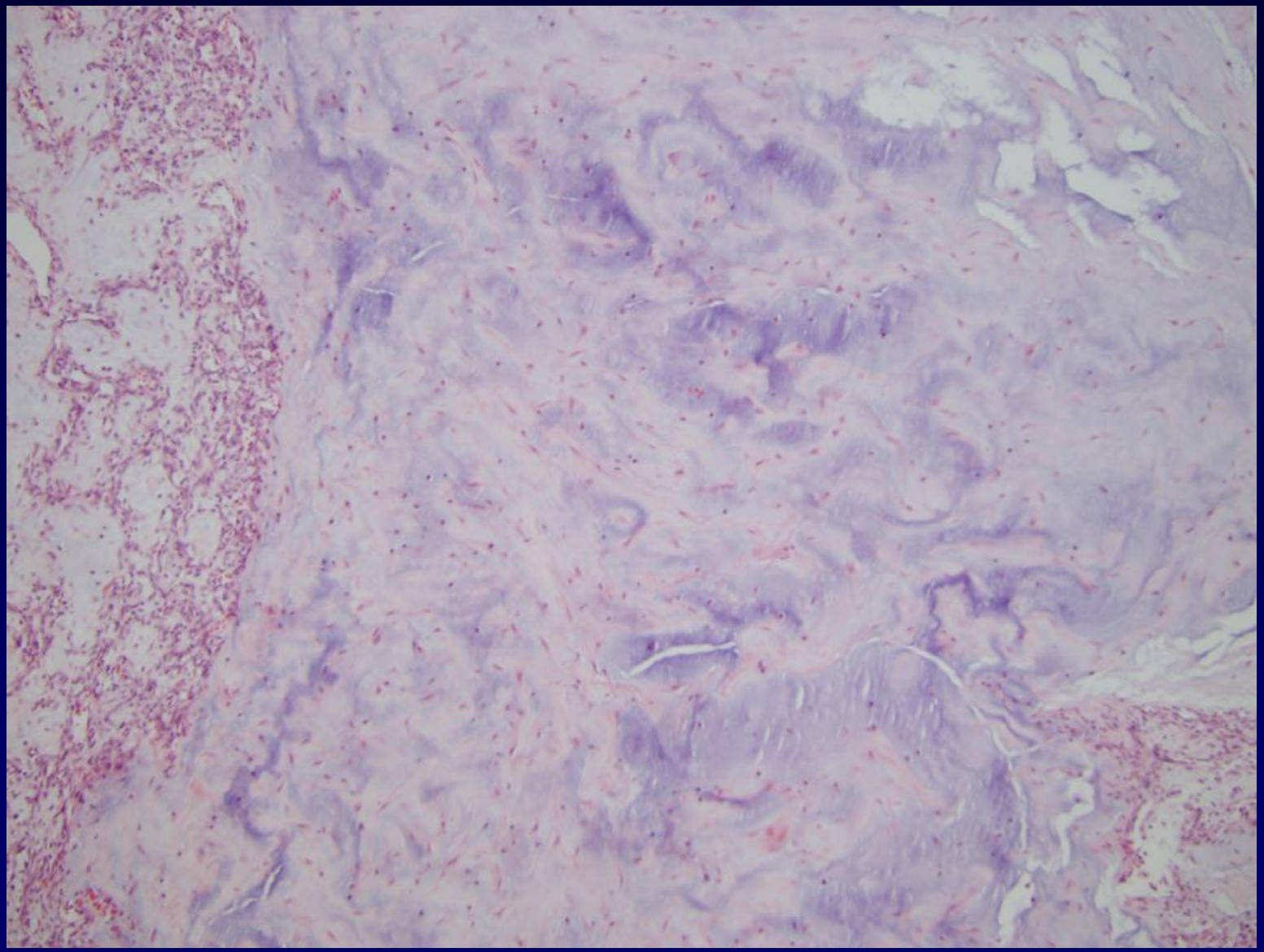
Umbilical Cord Hemangioma



Umbilical Cord Hemangioma



Umbilical Cord Hemangioma



Umbilical Cord Hemangioma

- Rare lesion
- Probably hamartoma not neoplasm
- Possible origin
  - Cord vessels
  - Vestigal vitelline vessels
  - Cord mesenchyme

Umbilical Cord Hemangioma

- Come to clinical attention
  - Mass on ultrasound
  - ↑ maternal AFP
  - Found at delivery
- Differential diagnosis
  - Hematoma
  - Teratoma
  - Omphalocele

Umbilical Cord Hemangioma

Fetal complications

- Stillbirth
- Preterm delivery
- Hydrops fetalis
- Severe fetal hemorrhage
- Intrauterine growth restriction
- Hemangiomas elsewhere